A Translational Systems Pharmacology Model for Aβ Kinetics in Mouse, Monkey, and Human

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A mechanistic model of amyloid beta production, degradation, and distribution was constructed for mouse, monkey, and human, calibrated and externally verified across multiple datasets. Simulations of single-dose avagacestat treatment demonstrate that the Aβ<sub>42</sub> brain inhibition may exceed that in cerebrospinal fluid (CSF). The dose that achieves 50% CSF Aβ<sub>40</sub> inhibition for humans (both healthy and with Alzheimer’s disease (AD)) is about 1 mpk, one order of magnitude lower than for mouse (10 mpk), mainly because of differences in pharmacokinetics. The predicted maximal percent of brain Aβ<sub>42</sub> inhibition after single-dose avagacestat is higher for AD subjects (about 60%) than for healthy individuals (about 45%). The probability of achieving a normal physiological level for Aβ<sub>42</sub> in brain (1 nM) during multiple avagacestat dosing can be increased by using a dosing regimen that achieves higher exposure. The proposed model allows prediction of brain pharmacodynamics for different species given differing dosing regimens.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
- Multiple AD treatments are developed targeting production of amyloid β, CSF and plasma Aβ are the main PD biomarkers in humans, so for understanding of brain PD, preclinical models are extensively used.

WHAT QUESTION DOES THIS STUDY ADDRESS?
- The questions this study address are 1) whether a mechanistic translational model can allow for prediction of short-term GSI pharmacodynamics in humans, and 2) what inhibition levels can be achieved in human brain, given the information on the system and drug PK.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
- The mechanistic model allows comprehensive comparison of different species revealing the difference in Aβ transport and production. Different sensitivities of brain and BIF Aβ to drug AUC requires a specific schedule to normalize brain Aβ.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
- Our model allows for more accurate translation of preclinical results to clinical data and optimization of therapeutic regimen. It provides a link between measured biomarkers and unobservable brain concentrations for estimation of the real drug effect on amyloid toxicity.

ORIGINAL ARTICLE

Cognitive decline in Alzheimer’s disease (AD) is usually preceded by the accumulation of the pathologic amyloid beta (Aβ) protein in the brain. Both insoluble and soluble forms of Aβ may be neurotoxic. In familial forms of AD, genetic mutations may be responsible for modified (increased or decreased) Aβ turnover.1 Other hypothesized mechanisms (e.g., tau pathology, inflammatory response, vascular and metabolic dysfunction<sup>2,3</sup>) for AD etiology are considered, but Aβ-related toxicity participates in most of them. The Aβ hypothesis is being tested in multiple clinical trials evaluating drugs that can alter Aβ kinetics in humans. Passive immunotherapy against Aβ is tested in trials of bapineuzumab by Elan,4 Solaneuzumab by Eli Lilly, and crenezumab and ganetemub by Roche/Genetech (Clinicaltrials.gov). Amyloid production inhibition efficacy is now tested for verubecestat by Merck, AZD-3293 by Astra Zeneca, and JNU-54861911 by Janssen. The influence on amyloid clearance pathways is tested for retinoid receptor agonists such as acitretin by Actavis/Allergan, and bexarotene by Ligand Pharmaceuticals. Gamma-secretase inhibitors (GSI) avagacestat by BMS and semagacestat by Eli Lilly have also been tested and have shown no success.

Aβ is produced primarily in the endosome and plasma membrane of neurons<sup>5</sup> and to a lesser extent in cells of other tissues.<sup>6,7</sup> Given the proximity of cerebrospinal fluid (CSF) to brain, for clinical trial purposes the change in the CSF Aβ level has been used as an indicator for brain Aβ modulation upon therapeutic intervention that targets brain Aβ production or clearance. Plasma Aβ has been monitored in early-stage clinical trials as a quick endpoint for assessment of peripheral pharmacological activity. However, the relationship between brain, CSF, and plasma Aβ is not straightforward, and peripheral pharmacological activity does not necessarily translate into central pharmacological activity. Depending on the class of therapeutic, different patterns of Aβ kinetics, in plasma and CSF, have been reported. A pronounced rebound in plasma Aβ concentrations was observed for GSI, avagacestat, and semagacestat, in human<sup>8,9</sup> and in mouse, in CSF for avagacestat doses 15–50 mg in humanes<sup>11</sup> and 30 mpk of...
Mechanisms of amyloid aggregation in BIF are not described, so this model is not applicable for longer-duration simulations and the mechanistic description of disease progression. The pathological AD state is treated as steady state with altered values of $A_{\beta}$ production$^{20,21}$ and clearance in brain (see details in Supplement A).

Interspecies scaling

Interspecies translation of model parameters was performed using allometric scaling (a generic equation as below):

$$P = P_0 \times \left(\frac{BW}{BW_0}\right)^n$$

where $P$ and $P_0$ are reaction rate constants of species with body weight $BW$ and $BW_0$, respectively, and $n$ is the scaling exponent. The allometric scaling alone may not allow for satisfactory translation from rodents to primates, so additional scaling coefficients for groups of processes were incorporated (Supplement A).

Model calibration and evaluation

The model calibration steps across different data types (Table 1) involved the Hooke-Jeeves method$^{22}$ implemented in the DBSolve Optimium package$^{23}$ v. 36.

To evaluate its predictive ability, the model was employed to replicate datasets that were not used in model development (Table 1) with consideration of respective study conditions. For fitting the mouse model, we chose $A_{\beta40}$ data in brain and CSF from an avagacestat dataset. The main goal was to describe human data as accurately as possible, so a human dataset (which is rich enough) was used for translation from rodents to primates: steady-state concentrations, SILK data, and GSI PD were fitted by scaling factors for $A_{\beta}$ production and distribution (Table S2); then a monkey dataset (steady-state values, SILK data) was used for external verification without scaling factor refitting. The semagacestat dataset$^{24}$ was chosen for calibration among GSI data, as it was complemented by SILK kinetic data, while avagacestat human PD data were used for external verification.

Description of PK of avagacestat and semagacestat

The PK time courses that drove the systems model for avagacestat and semagacestat were implemented using compartmental PK modeling or explicit functions where appropriate (see Supplement B) for reproduction of observed PK data. Values of $IC_{50}$ measured $in vitro$ were used in equations for $\gamma$-secretase inhibition (Supplement A,B). Due to lack of the brain PK data, we assumed for simplicity brain PK profiles analogous to plasma profiles with correction for brain penetration coefficients.

A full description of experimental facts and model assumptions, ODE system, rate laws, values of model parameters, and experimental data used for model calibration and validation is given in the Supplementary Materials.

Simulation design

Details of design of simulations to explore model behaviors, analyze properties of the system, and optimize therapeutic regimen are provided in Supplement C.
Figure 1: Schematic representation of processes considered in the model. (a) Processes related to endogenous Aβ. Dashed arrows stand for transport with bulk flow. Solid arrows designate reactions, biosynthesis, degradations and transport mediated by proteins (uptake, efflux, and transcytosis). List of abbreviations: C99BC, C99BIF, C99OT are C99 in brain cells (BC), brain interstitial fluid (BIF) and other tissues (OT), respectively. A40BC, A40BIF, A40CSF, A40PL, A40OT are Aβ40 in BC, BIF, CSF, PL, and OT, respectively. Processes designation: synthesis of amyloid β precursor protein C99 in BC, BIF, OT; VrelBC, VrelBIF, VrelOT, respectively; transformation of C99 to Aβ (Aβ hereafter refers to both Aβ40 and Aβ42 unless specified) catalyzed by γ-secretase in BC, BIF, and OT (processes Vgs40BC, Vgs40BIF, Vgs40OT); bulk phase (nonreceptor-mediated) degradation of Aβ in BC, BIF, and OT (processes Vdeg40BC, Vdeg40BIF, Vdeg40OT); transport of Aβ between BC and BIF (processes Vtr40BIFBC); transport of Aβ with bulk flow from BIF to cerebrospinal fluid (CSF), from BIF to plasma (PL) and from CSF to PL (processes Vflow40BIFCSF, Vflow40BIFPL, Vflow40CSFPL); protein-mediated transport of Aβ via BBB (between PL and BIF), via BCSFB (between PL and CSF) and between PL and OT (processes Vtr40PLBIF, Vtr40PLCSF, Vtr40PLOT); degradation of Aβ during passage through BBB (between PL and BIF), BCSFB (between PL and CSF) and between PL and OT (processes Vdeg40PLBIF, Vdeg40PLCSF, Vdeg40PLOT). (b) Complete scheme of the model for all species: left part, endogenous Aβ species; right, labeled Aβ. Processes are analogous to (a), but names are not given for simplification. Red asterisk indicates 13C-label or 125I-label. List of abbreviations: C99BC, C99BIF, C99CSF, C99PL, C99OT are endogenous and 13C-labeled C99 in BC, BIF, and OT, respectively. A40BC, A40BIF, A40CSF, A40PL, A40OT, A42BC, A42BIF, A42CSF, A42PL, A42OT are endogenous and 13C-labeled (125I-labeled) Aβ40 in BC, BIF, CSF, PL, and OT, respectively. A42BC, A42BIF, A42CSF, A42PL, A42OT are endogenous and 13C-labeled (125I-labeled) Aβ42 in BC, BIF, CSF, PL, and OT, respectively.
RESULTS
Model calibration and verification
Aβ kinetics and steady state in different species. The model satisfactorily reproduces the mouse steady-state Aβ concentrations in different compartments (Figure 2a), mouse avagacestat PD, the phase shift between brain and CSF Aβ_42, the overshoot in CSF and plasma Aβ concentrations before returning to baseline level (Figure 2b), and correctly reproduces the amplitude of Aβ_42 decrease.

The model adequately describes the difference of Aβ_42 brain and CSF concentrations between healthy and AD individuals (Figure 3). Concentration of Aβ_42 in healthy control human brain (Figure 3) are similar to those of mouse (Figure 2a), but CSF Aβ_42 is higher (more than 1 nM in healthy human vs. about 0.3 nM in mouse). Production and clearance of Aβ as measured by SILK data are also captured by the model (Supplement B).

Different variants of BW-independent scaling parameters of synthesis, enzymatic, and transport reactions were tested. Satisfactory results were obtained by fitting 11 parameters for interspecies scaling (Table S2 of Supplement) and four parameters for scaling from healthy to AD state as specified in “Methods” (Table 2). Five parameters (Table 2) describe scaling from mouse to human and thus illustrate the magnitude of difference in Aβ synthesis between species.

After translation to primates, the model was externally verified on monkey data: body weight based allometric scaling alone was sufficient to describe the data (Figure 3a, Supplemental Figure B11).

Description of human GSI data. GSI treatment prediction performance was verified comparing the clinical avagacestat single dose data for healthy individuals (Figure 3b) with simulations of treatment at an IC50 value measured in...
vitro, and measured PBPK parameters (Table S2). Data for Aβ PD during GSI treatment often demonstrate strong fluctuations, which may be explained partially by diurnal Aβ oscillations, which were not accounted for in the model. However, the amplitude of inhibition (minimum of PD curve) falls within the 95% prediction band for each of measured quantities, except for Aβ42 inhibition, and exceeds the accuracy of prediction achieved in the work of Niva et al. We conclude that this model satisfactorily predicts inhibition.

Insights from simulations and implications for drug discovery and development

CSF and brain Aβ40 inhibition in human vs. mouse. We simulated the Aβ response to single-dose avagacestat administration in the mouse and human (analogous to those presented in Figures 2b, 3b) to study the dependence of PD characteristics on dose and area under the curve (AUC). Model predictions were compared (Figure 4) to data used for fitting (mouse Aβ40 data) and

Figure 2 Verification of the model on the mouse data. (a) Steady state concentrations of Aβ40 and Aβ42 in mouse brain, CSF, and PL. Experimental data were taken from Ref. 45. Bars for experiments represent mean from across different animals (from 6 to 60 animals for different data items), bars for model represent average population model prediction. (b) Aβ40 (expressed in % of steady state baseline level) in brain, CSF, and plasma, and Aβ42 in brain in the mouse treated with a single dose of 30 or 150 mg/kg of avagacestat. Symbols represent data and curves model simulations. Plasma Aβ40 and brain Aβ42 were not used during the fitting.

Figure 3 Verification of the model on the human and monkey data. (a) Steady-state concentrations of Aβ40 and Aβ42 in brain, CSF, and PL for healthy (green) and AD (red) humans (used for fitting) and monkey (yellow, not used for fitting) predicted by the model (95% CI). Prediction for monkey was obtained by allometric scaling from human model. Experimental data (points with SE) were taken from Refs. 27–31,45–59. (b) Verification of the model against avagacestat data. Time dependence of Aβ40, Aβ42 in CSF and Aβ40 in plasma resulted from single administration of 50, 200 and 400 mg of avagacestat to healthy subjects. Aβ40 is expressed as % of steady state base level (placebo adjusted). Dots correspond to measured data taken from Refs. 8,11,17,50; lines denote confidence bands and median calculated by the model and Hessian for human-fitted parameters.
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Table 2 Selected parameters describing differences between mouse and healthy and AD individuals

| Parameter | Description | Factor for healthy humans (95% CI) | Factor for AD humans (95% CI) |
|-----------|-------------|-----------------------------------|-------------------------------|
| VmaxGS<sub>BC</sub>/<sub>hm</sub> | Scaling factor for gamma secretase Vmax in BC | 1.01 (0.34–2.86) | 32<sup>a</sup> |
| VmaxGS<sub>BIF</sub>/<sub>hm</sub> | Scaling factor for gamma secretase Vmax in BIF | 8850 (4531–17278) | 8850 (4531–17278)<sup>c</sup> |
| Vrel<sub>BC</sub>/<sub>hm</sub> | Scaling factor for rate of Aβ precursor release in BC | 0.534 (0.28–1.01) | 5.18 (1.27–21.02) |
| Vrel<sub>BIF</sub>/<sub>hm</sub> | Scaling factor for rate of Aβ precursor release in BIF | 4.55 (3.34–6.21) | 5.18 (1.27–21.02)<sup>c</sup> |
| portion<sub>BC</sub>/<sub>40–42hm</sub> | Scaling factor for proportion of Aβ<sub>40–42</sub>/Aβ<sub>40</sub> synthesis in BC | 13000 (2300–84269) | 15 (3.65–63.67) |
| kpc<sub>BC</sub>/<sub>40</sub> | Dummy polymerization rate constant of Aβ<sub>40</sub> | 0 | 0.87 (0.01–56.08) |
| kpc<sub>BIF</sub>/<sub>40</sub> | Dummy polymerization rate constant of Aβ<sub>40</sub> | 0 | 1.0 (0.02–57.2) |

Example of equation for calculation of rate for production in BC in human is below: Vrel<sub>BC</sub>=Vrel<sub>BC</sub><sup>0</sup>/C<sub>0</sub>C<sub>1</sub><sup>6</sup>/C<sub>1</sub><sup>7</sup>, where function swrel<sub>BC</sub>=sw<sub>BC</sub><sup>0</sup>+<sub>ADsw<sub>BC</sub></sub><sup>0</sup> where function swrel<sub>BC</sub>=sw<sub>BC</sub><sup>0</sup><sub>ADsw</sub><sup>0</sup> where function swrel<sub>BC</sub>=sw<sub>BC</sub><sup>0</sup>. The model simulations of the Aβ<sub>42</sub> inhibition in points not used for fitting; and 4) brain inhibition is lower than CSF for high dosages for all species.

Extrapolation from Aβ<sub>40</sub> to Aβ<sub>42</sub> pharmacodynamics. The Aβ<sub>42</sub> PD data were not used for calibration of the model. The model simulations of the Aβ<sub>42</sub> compartments tend to underestimate CSF Aβ<sub>42</sub> inhibition (human data, Figure 4a) and overestimate brain inhibition (mouse data). It appears that Aβ<sub>42</sub> was not predicted satisfactorily based on Aβ<sub>40</sub> data fitting even for the same species (mouse).

Exploration of exposure-effect relationships. The resulting drug exposures corresponding to the observed single-dose PD effects were similar for all species for brain Aβ<sub>40</sub> inhibition (Figure 4b). The differences in IC<sub>50</sub> (Figure 4a) between mouse and human are driven in part by species-related PK properties. The large difference in CSF Aβ<sub>40</sub> responses, as captured by area under the effect curves (AUEC) (Figure 4b), may depend on production in other tissues (see details in Supplement C).

Efficacy of GSI on Aβ levels in the AD population compared with healthy individuals. To understand what potential therapeutic effects could be achieved on neuronal function and survival, we simulated inhibition for a range of dosages and compared the results with in vitro literature data describing the influence of Aβ on neuronal function. In vitro experiments suggest the enhancement of LTP (long-term potentiation) in the presence of Aβ<sub>42</sub> with a maximal effect around 200 PM and decrease of this effect for concentrations below 20 PM. These values correspond well with observed physiological levels of BIF Aβ<sub>42</sub>. We assumed that the Aβ<sub>42</sub> concentration optimum for neural function in vitro would be similar as derived from in vitro experiments and should not decrease below ~10 PM. Significant cytoxicity was observed at levels of intracellular soluble Aβ<sub>42</sub> exceeding 1 nM. This conforms to the fact that the steady-state brain concentrations of Aβ<sub>42</sub> in healthy humans and mice are below 1 nM, while for AD subjects Aβ<sub>42</sub> exceeds 1 nM (Figures 2a, 3a). We have specified in our simulations that 1 nM in brain cells would be the reference level for toxicity. Semagacestat and avagacestat demonstrate similar dose dependence for BIF Aβ inhibition in AD subjects during 3 days (Figure 5a). A significant difference between drug efficacy (semagacestat vs. avagacestat) is observed for BC inhibition (Figure 5a), bottom, with the central tendency of returning BC Aβ<sub>42</sub> concentrations to physiological values. The 95% prediction confidence band for the brain Aβ<sub>42</sub> inhibition by semagacestat reaches the region of safe concentration only at the highest doses simulated (Figure 5a). For avagacestat, the median reaches 1 nM corresponding to ~80% inhibition of Aβ<sub>42</sub> concentration from about 8 nM at steady state level in brain for AD subjects (Figure 5b).

Analysis of different GSI therapeutic regimens. Brain AUEC is more sensitive to plasma AUC than CSF AUEC at moderate doses (Figure 4) according to model predictions. This is explained through the model given the different dynamics of inhibition: Brain Aβ inhibition follows Aβ inhibition in CSF with some delay (Supplemental Figure C1), and both of them are delayed with respect to maximal drug concentration and maximal plasma inhibition. An optimized dosing regimen could lead to a potential therapeutic benefit due to higher AUC. We simulated 3 days of avagacestat treatment (analogous to previous section) with different dosing regimens. All simulated regimens with multiple daily dosing, even with a lower daily dose, provide better brain pharmacodynamics than the single dosing regimen (Figure 5b). The forecasted brain cell Aβ<sub>42</sub> concentrations fell below 1 nM on the third day of simulated therapy. Moreover, each regimen provided enough safety, as the minimal BIF concentration
Figure 4 Comparison of avagacestat dose-effect (a) and exposure-response (b) relationships for mouse and humans (healthy and AD individuals). (a) Dose dependence of amplitude of $A_{40}$ and $A_{42}$ decrease resulting from single dose administration of avagacestat (expressed as % of steady state base level) in mouse (green line) healthy human (blue line), and AD human in brain (red line) and CSF; (b) dependence of $A_{42}$ and $A_{40}$ AUEC (area under effect curve) from avagacestat AUC (area under curve for concentration). Symbols correspond to measured data: circles correspond to data used for fitting, crosses correspond to measured data for validation of human CSF predictions.6,11,17,50 and mouse brain A$A_{42}$.10 did not fall below the normal range of values. A q.d. regimen has the lowest AUC (Figure 5c) even when compared with lower total daily dosing regimens. Higher AUC lead to higher maximal BC amyloid inhibition, but not maximal BIF inhibition.

DISCUSSION

The purpose of this study was 1) to apply the model to evaluate contributions of different sources of $A_{40}$ (synthesis in brain and other tissues) to its level in brain cells, brain interstitial fluid, CSF, and plasma; 2) to explore the translation of GSI mechanistic dynamics across mouse, monkey, and human species; and 3) to identify GSI administration regimens that would return $A_{40}$ to normal human (non-AD) levels.

The developed model satisfactorily describes the kinetics of $A_{40}$ distribution and steady-state levels in mouse, monkey, and human (healthy subjects and AD patients).

Model calibration efforts confirmed that conventional allometric scaling, of reaction rates, was not sufficient to translate the model from mouse to humans, reflecting that significant differences exist between these species that may not be explained solely by body weight. They relate not only to the production of $A_{40}$, but also to its degradation and transport. Dissimilarity of these processes between species was found in three parameters other than for $A_{40}$ production. Bulk flow from BIF to CSF in humans differs by an order of magnitude from the value calculated by allometric scaling, reflecting possible involvement of other mechanisms in brain $A_{40}$ fluxes. Plasma-CSF $A_{40}$ exchange is greater in humans according to the model, suggesting possible differences in BCSFB architecture across species. In contrast to mouse-human translation, body weight-based allometric scaling is sufficient for the translation between human and monkey, therefore the monkey may be a better preclinical in vivo model for biomarker translation.

The $A_{42}/A_{40}$ ratio is higher in human brain than in plasma and CSF (see Figure 3 with illustration of data from different references27–31). Moreover, the CSF $A_{40}$ level is much higher in humans than in mouse, while brain concentrations are similar. Plasma $A_{40}$ concentrations in human and mouse are similar (about 0.05 nM, Figures 2a, 3a), thus the higher $A_{40}$ level in human CSF reflects higher brain production. Higher $A_{42}$ level in human brain should reflect reduction of the portion of $A_{40}$ produced in brain cells. A balance between increase of $A_{42}/A_{40}$ in brain and high CSF $A_{40}$ level leads to a higher parameter value of $A_{40}$ in humans (Table 2). The possibility that the higher level of CSF $A_{40}$ in humans is due to lower degradation seems unlikely, as the model correctly describes $A_{40}$ clearance after GSI administration. Many minor differences may exist between mouse and humans, but we have chosen only a few parameters identifiable given the dataset. According to the same reasoning, the AD state may be a result of slight changes in an extended set of processes, but here it was described by changing production and/or degradation, so calibration only on baseline data allows for determining only some effective parameters. This is an important limitation, which should further be eliminated by extension of calibration on new PD data.33

GSI treatment maximal effect is reproduced by the model, but some dynamic properties were not accurately described. The overshoot for human $A_{40}$ plasma concentration is underestimated for semagacestat (Supplement Figure B9) and
low doses of avagacestat (Figure 3b) and overestimated for higher avagacestat doses (Figure 3b). Model predictions for CSF Aβ show a similar pattern but do not completely follow the data.

Problems with the PD description are observed in the mouse also (Figure 2b): both brain and CSF curves predicted by the model lag behind the measured points during the decline phase. It can be assumed that the description of distribution between BIF and brain cells is simplified: exchange between these compartments is carried out by different mechanisms, including endocytosis and exocytosis, while there is one hypothetical carrier in our model responsible for transport. Another possible explanation is that drug IC50 values measured in vitro may not reflect the physiological situation.

Comparison of the inhibition amplitudes in different species (Figure 4) leads us to the conclusion that CSF Aβ40 has approximately the same biomarker capacity for humans and mouse, slightly overestimating brain inhibition (for AD

**Figure 5** Simulations of Aβ42 (given in nM) maximal inhibition during multiple dosing (3 days) in AD subjects. (a) Comparison of predicted confidence bands (obtained by 4,200 replicates from log-normal distribution of parameters using Hessian matrix) for BC and BIF Aβ42 minimal concentrations during 3 days of GSI administration once daily with levels supposed to be safe (or normal). Solid and dashed lines, confidence bands calculated by the model; colored regions, regions of physiologically safe values. Calculations were made for doses from 5 mg to 10,000 mg. (b) Simulation of Aβ42 inhibition dynamics for 3 days of different dosing regimens of avagacestat: comparison of Aβ42 in BC (upper panel) and BIF (lower panel) with normal values; q.d., once a day; b.i.d., twice a day; t.i.d., three times a day; q.i.d., four times a day. (c) AUC for different avagacestat dosing regimens.
subjects CSF 75% Aβ40 inhibition corresponds to ~60% brain Aβ40 inhibition for avagacestat dose of 10 mpk). Healthy subject CSF data underestimate the potential CSF inhibition level for AD subjects. Avagacestat doses of ~2 mpk would lead to about 55% inhibition of Aβ40 in CSF of healthy controls, while about 65% inhibition in CSF and 50% inhibition in brain are predicted for AD subjects. Clinically tested dosages (below 150 mg avagacestat for AD36) do not allow achieving a normal concentration (Figure 5a), but may lead to a BIF Aβ concentration decrease below the physiological level.

Aβ42 pharmacodynamics for one GSI (e.g., avagacestat) cannot be predicted based on the PD data for Aβ40 or Aβ42 from another GSI (e.g., semagacestat) directly (Figure 3) even for the same species (mouse or human). In our model GSI acts on the total secretase rate, and so Aβ pharmacodynamics is determined by such system properties as proportions of Aβ40/42 synthesis in different compartments and clearance (distribution). To describe higher inhibition of Aβ42, we should suppose a specific mechanism leading to changes in the proportion of Aβ40/42 production: drug interaction with presenilin37 or detailed analysis of drug action in different intracellular compartments. Analysis of AUEC and AUC (Figure 4b) have shown that even the exposure–response relationship difference between species will not be explained by PK properties only and, moreover, the difference in the brain Aβ42 inhibition between AD and healthy individuals should be expected.

A difference in the exposure–response relationship between brain and CSF (Figure 4, Supplement Figure C2) is expected to be due to the different Aβ half-lives in brain and plasma and different contributions of plasma amyloid to brain and CSF (Supplement Figure C1). The overshoots of CSF Aβ concentration, predicted for all species, may originate simply from γ-secretase substrate accumulation in our model, as we do not consider more complex enzymology.38 It is similar in general to the mechanism proposed previously,39 assuming overwhelmed γ-secretase processing by C99 and increased APP pool. Slight overshoot in the brain is observed only for healthy subjects probably because of the different relationship between synthesis and degradation of Aβ (Table 2, Table S2).

Soluble nonfibrillar Aβ has been demonstrated to be more toxic to neurons than the aggregated form.26,40,41 The model presented here allows for direct comparison of the concentrations of soluble amyloid species, forecast from the model, and the proposed toxicity thresholds as defined by in vitro studies in such inaccessible compartments as BIF and even brain cells. It could facilitate understanding the reasons for the failure of many GSI clinical trials. PD simulations for a long time require: 1) more accurate PK description, as differences between PK on days 1 and 7 have been shown11; 2) description of amyloid aggregation and accumulation processes; 3) disease progression description. As all of these considerations are out of the scope of this analysis, we simulated PD for only 3 days of treatment and assumed that it will give a rough estimate of the results of trials, which can later be compared with the results of an extended model. Achieving brain Aβ levels corresponding to normal concentrations (Figure 5a) requires very high avagacestat dosages conjugated with a risk of decrease below an optimal BIF level of Aβ. This effect, if it exists in vivo, would be independent of the mechanism of production inhibition (BACE or GS inhibition), as it is related to Aβ level decrease, but not to other pathways, e.g., Notch signaling inhibition, observed for semagacestat,42 or substrate accumulation.43 Saturation of effect at avagacestat dosages higher than 5,000 mg may be due to a decrease in bioavailability for higher dosages and absorption saturation assumed in the model (Supplement B.1). Differences between brain efficacy of semagacestat vs. avagacestat are due to the distinct plasma–brain penetration coefficients (0.05 for semagacestat vs. 4.35 for avagacestat10) and different PK profiles: long decay (Figure 2(b), Supplement) together with high brain penetration and low IC50 of avagacestat allows retaining substantial brain inhibition for a much longer period of time. Our simulations have shown the importance of higher AUC for brain inhibition, but not for BIF inhibition (Figures 4, 5), suggesting that PK properties are significant for brain PD.

The reason for the different dynamics in BIF and BC may be the exchange between BC and BIF: in the model, the equilibrium constant between rates of uptake and release was fitted to 10, in line with observed extensive uptake,44 which leads to faster depletion of BIF Aβ. Both brain and BIF concentrations depend mainly on brain production, and thus, the only way to provide a positive difference in BC and BIF PD, besides the specific dosing regimens, would be the development of a compound with a different intra- and extracellular IC50 or a drug influencing intra- and extraneuronal amyloid transport. Compounds should have a lower clearance rate to be able to retain high drug plasma concentrations for a longer period of time.

CONCLUSION

The proposed model can be considered a framework for exploration of the amyloid system, translating between species, hypothesis generation, and understanding therapeutic options targeting this system. Key problems in construction of this model are the choice of datasets that are optimal for model fitting and external verification, and handling multiple datasets and analyzing accuracy of predictions.

In the accompanying article, we extend our Aβ distribution model in such way as to take into account Aβ40 and Aβ42 aggregation with longitudinal time effects to describe AD progression over the decades.

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Supplementary information accompanies this paper on the CPT: Pharmacometrics & Systems Pharmacology website (http://psp-journal.com).