

Introduction

- Nucleoside analogues like acyclovir (ACV) and ganciclovir (GCV), require intracellular phosphorylation into active metabolites for inhibition of viral replication¹.
- Active transport at the level of brain cell membrane or pathological changes might affect intracellular PK of active metabolites².
- For viral CNS infection, we have limited understanding of the PK of these triphosphates inside brain cells. Data from brain extracellular (ECF) or plasma might be misleading for understanding drug target site PK².
- LeiCNS-PK3.0 adequately predicts drug PK profiles across different CNS regions³. However, two mechanisms critical for the PK evaluation of antivirals have not yet been included:
 - active transport across brain cell membranes.
 - intracellular conversion to active metabolites for better linking to drug efficacy.

Aim

- To extend the LeiCNS-PK 3.0 model so that it can predict intracellular triphosphate exposure of ACV and GCV.

Methods

- We built LeiCNS-PK3.2 from LeiCNS-PK3.0, by adding (i) active transport at the brain-cell membrane and (ii) intracellular conversion of ACV and GCV to their triphosphates (**Fig 1**).
- Rat and human PK data in plasma and in cerebrospinal fluid (CSF) in the subarachnoid space were extracted from literature for model validation⁴⁻⁷.
- Brain ECF and intracellular fluid (ICF) PK were simulated over the first five standard doses.

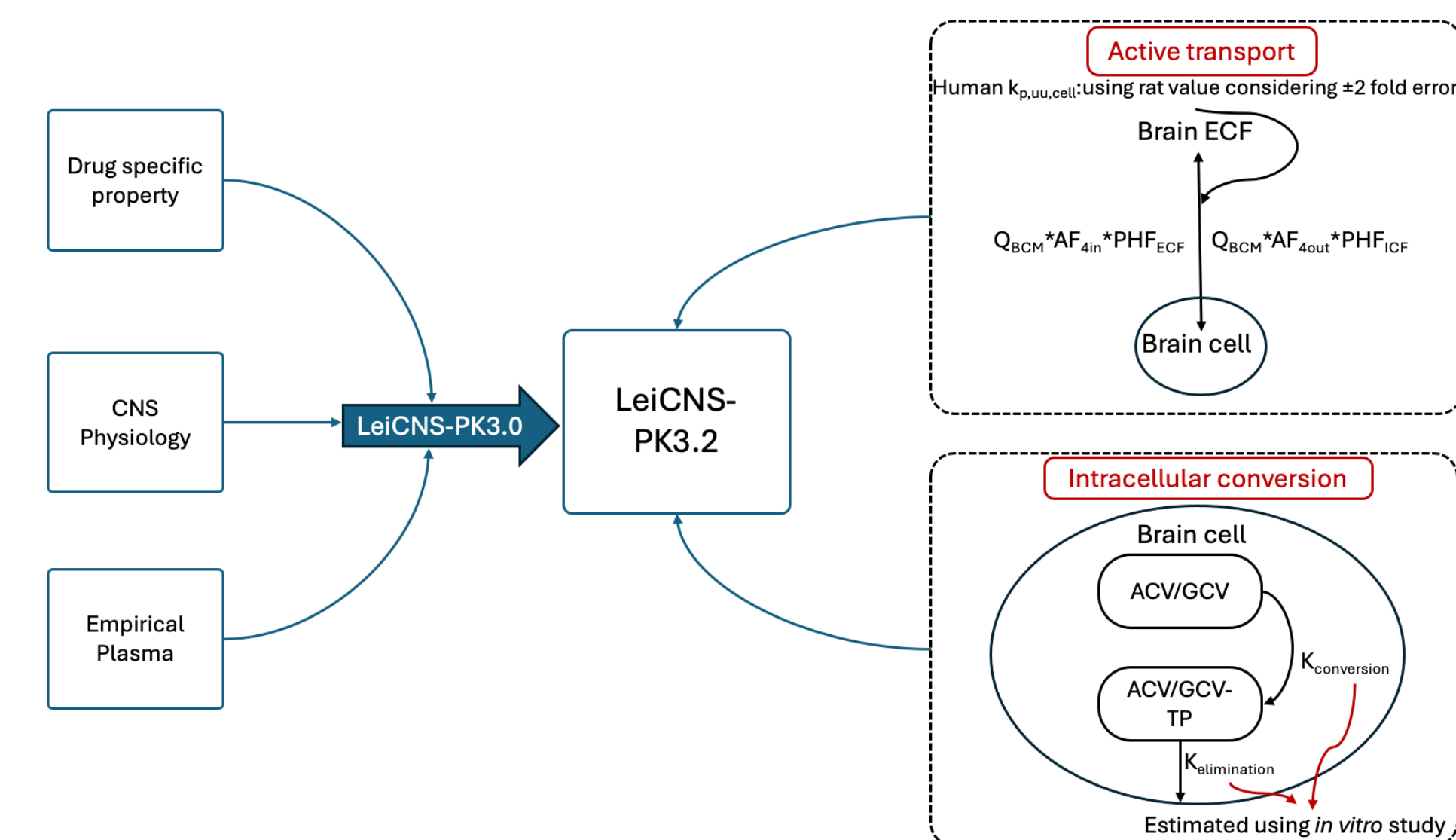


Fig 1. Schematic presentation of the LeiCNS-PK3.2 model construction. LeiCNS-PK3.2 extends from LeiCNS-PK3.0 by incorporating two novel mechanistic components: active transport across the brain cell membrane (top box) and intracellular metabolic conversion of ACV and GCV to their triphosphates (bottom box).

Results

❖ LeiCNS-PK3.2 successfully predicts observed ACV and GCV data

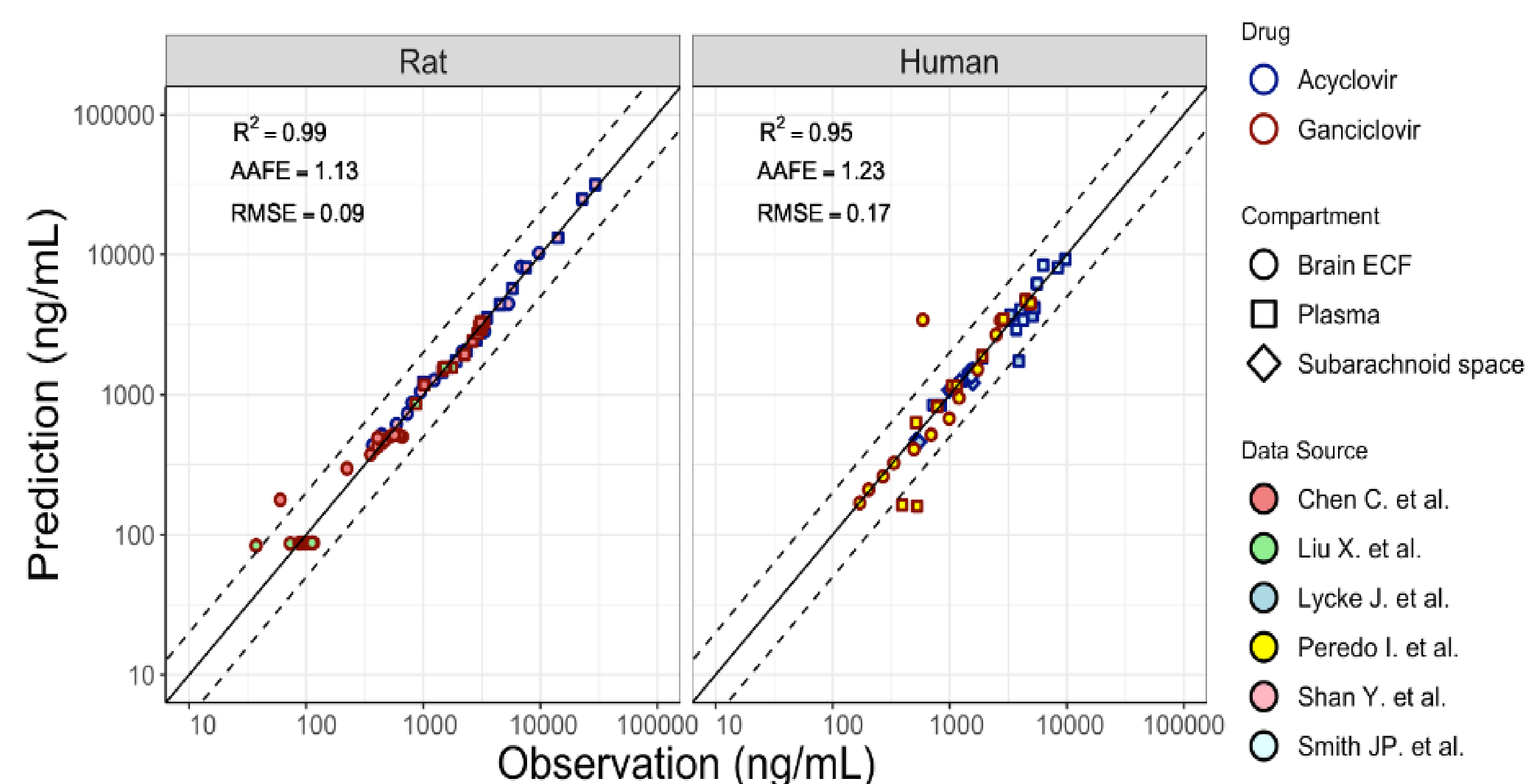


Fig 2. Observed vs. predicted PK of ACV and GCV in rat and human. Correlation between observed and model-simulated concentrations of ACV and GCV, shown for rat (left panel) and human (right panel) datasets. Observations include ACV and GCV data from plasma, brain ECF, and CSF in the subarachnoid space.

Data sources from literature are highlighted in the legend. Solid diagonal lines represent perfect agreement; dashed lines indicate a 2-fold prediction error. Model performance metrics, including the coefficient of determination (R^2), average absolute fold error (AAFE), and root mean square error (RMSE), are shown within each panel.

❖ Altering pathological-related parameters did not affect drug PK

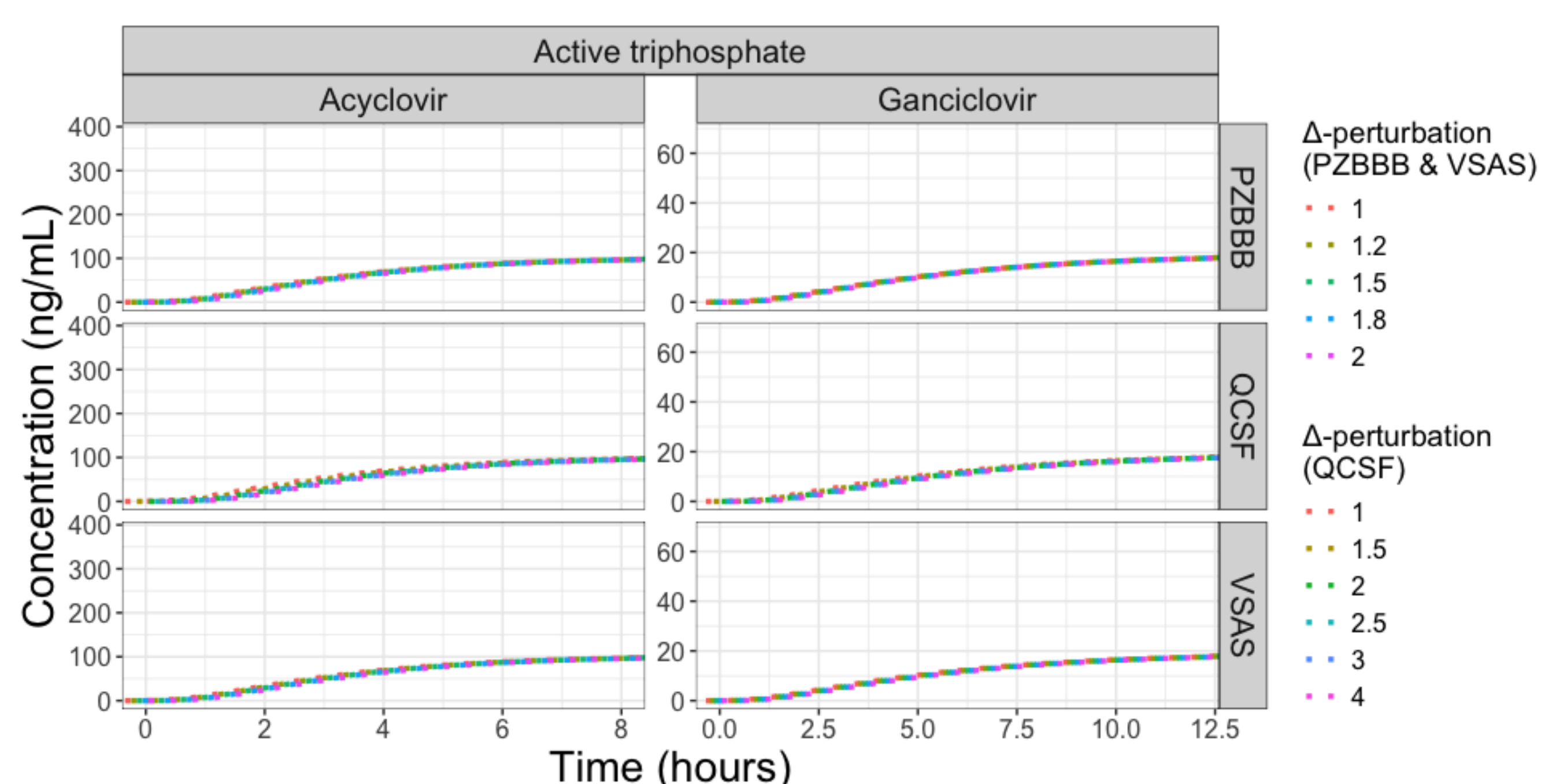


Fig 4. Sensitivity analysis of intracellular metabolite PK in LeiCNS-PK3.2. Predicted active triphosphate metabolite PK in brain ICF for ACV and GCV across varying perturbation levels (Δ) of pathological-related parameters (PZBBB: pore size of blood-brain barrier; QCSF: CSF flow rate and VSAS: volume of subarachnoid space).

❖ Different exposures were observed between brain ECF and ICF at standard drug dosing

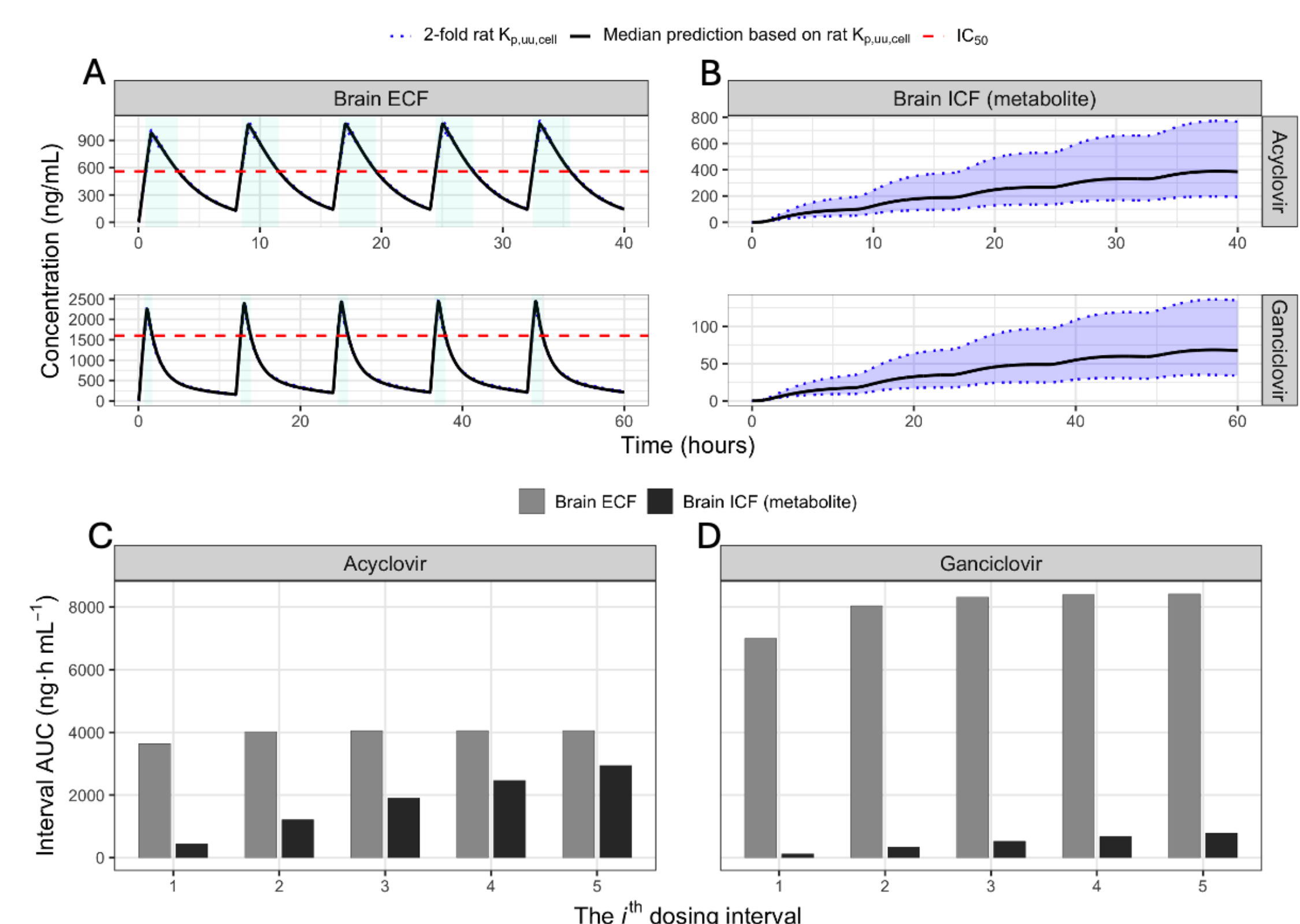


Fig 3. Simulation-based comparison of brain ECF and ICF PK for standard dosing regimens (ACV: 10 mg/kg, 3- daily; GCV: 5 mg/kg, 2-daily). Upper panels illustrate the PK of ACV and GCV in brain ECF and their respective active triphosphate metabolites in brain ICF. The shaded areas with dotted line boundary represent the uncertainty range ($\pm$ 2-fold $K_{p,uu,cell}$) around median predictions. Red dashed lines denote the IC50 values. Lower panels present interval AUC for the first five dosing intervals—prodrugs in the brain ECF has higher AUC values and reaches SS faster than brain ICF triphosphate.

Conclusions

- Active triphosphate brain ICF PK differs markedly from parent-drug exposure in brain ECF, indicating that brain ECF might not be a good surrogate for investigating intracellular metabolite exposure (**Fig 3**).
- Pathological changes may not affect antiviral metabolite PK (**Fig 4**).
- Quantitative PK/PD targets based on brain ICF and human-specific parameter like $K_{p,uu,cell}$ values are still lacking.

References

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