# Determination of brain histidine concentrations and kinetic modeling of human blood brain barrier transport

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## Introduction

Magnetic resonance spectroscopy (MRS) has been shown to be valuable for the determination of transport mechanisms at the blood-brain barrier (BBB) in the case of phenylalanine in phenylketonuria patients [1]. In this work, the same BBB amino acid (AA) carrier is studied for histidine (His) transport across the BBB in healthy subjects using 1H-MRS of His after an oral His load [2].

## Methods

Eight volunteers (4m/4f, 27±6 years old) received a single load of 400mg/$kg_{bw}$ of His and continuous blood and brain His concentration monitoring via blood sampling and MRS. Details of measurements and data fitting to obtain arbitrary institutional units have been described before [3] (3 T scanner, PRESS 20 ms TE, simultaneous fitting [per subject] of constant background signals and variable His contributions). Absolute brain concentrations were now determined with internal brain water as reference (excluding CSF) and separately determined $T_1$ and $T_2$ of His (obtained in one additional subject under His load). The course of blood and brain His content was modeled with symmetric and asymmetric Michaelis-Menten (MM) kinetics with and without parameter boundaries. A non-linear least squares fitting technique, implemented in MATLAB, was used by solving the ordinary differential equations with plasma His content interpolated to 1 min intervals. The pre-load brain His concentration (below MRS sensitivity) was estimated by iterative solving of the steady state and dynamic condition. Kinetic estimations were done in 3 ways: a) for data averaged over all subjects, b) for individual subjects (parameters averaged), c) in a simultaneous fit for all subjects with a common parameter set.

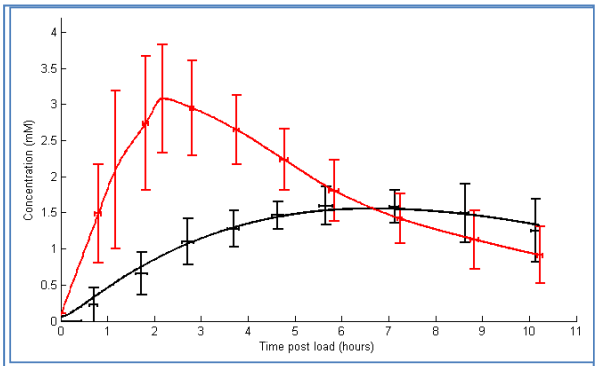


***Fig. 1*** *Averaged course of blood (red) and brain (black) [His] fitted in a symmetric kinetic model (black).*

## Results & Discussion

Relaxation times of brain His were found to be 1.4 s for $T_1$ and 72 ms for $T_2$. The absolute concentrations of His reached maximum values of 1.2 to 1.9 mM after the oral His load. Measurement uncertainties (Cramer Rao bounds) at individual time points were ~ 0.14 mM, independent of His content. The averaged data fitted well with the symmetric MM model (Fig. 1) yielding the following kinetic parameters: maximum transport capacity ($V^{max}$) 23 nmol/g/min, apparent Michaelis constant ($K_m^{app}$) 2.1 mM, cerebral metabolization rate (CMR) 0.3 nmol/g/min. $K_m^{app}$ translates to a theoretical absolute $K_m$ (valid in the absence of competing AA) of 0.6 mM (assuming transporter competition for the L1 carrier for large neutral amino acids (LNAA) only). $K_m$ and $V^{max}$ are similar to data obtained in rats [4]. Individual kinetic fits and the common fit deviated markedly from the fit results of the pre-averaged data hinting at the existence of individual differences, the inadequacy of the simple symmetric model, or the sensitivity of the model to small systematic errors in individual data. Two individual time courses illustrating these differences are plotted in Fig. 2, one with apparently fast kinetics (subj. 3), i.e. fast in- and out-flow; and another (subj. 2) with slow kinetics. The black curve corresponds to the best fit of the individual data, the blue curve represents the time course for these subjects with kinetic parameters from the fit of all data to a common parameter set. The data was also fitted with asymmetric models; one where the asymmetry originates from the individual courses of the other LNAAs in blood, the others more general asymmetric models. The former leads to a slightly worse fit of the data, while the latter improve the fit quality.

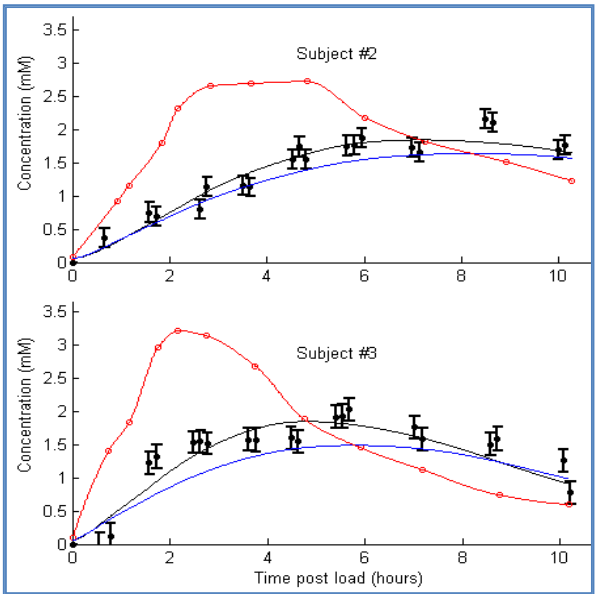


***Fig. 2*** *Individual course of brain and blood (red) His content for 2 subjects, incl. individual fits (black) and the fit using a common model for all subjects (blue).*

## Conclusions

Histidine transport kinetics was successfully determined with an apparent affinity of 2.1 mM and maximum transport velocity of 23 nmol/g/min in a symmetric MM model. However, due to the complexity of the system with multiple potentially relevant transport systems, multiple effective brain compartments, and a limited number of investigated subjects, the study is presently inconclusive regarding the most appropriate MM model and the relevance of inter-individual differences.

## References

**1.** Moller et al. *J Cereb Blood Flow Metab* 18:1184 (1998). **2**. Vermathen et al *MRM* 43:665 (2000). **3**. Chong et al. 17th *ISMRM 2009* 2346. **4**. Smith et al J Neurochem 49:1651 (1987)

*Supported by Swiss National Science Foundation (31-103938, 32_120324)*