

Quantifying myelin kinetics in healthy subjects using deuterium labeling.



Authors: K.M.S. Kanhai¹, S.C. Goulooze¹, J. Stevens¹, J.L. Hay¹, G. Dent², A.Verma², T. Hankemeier³, T. de Boer⁴, H. Meijering⁴, J.C. Chavez², G.J. Groeneveld¹

¹Centre for Human Drug Research, Leiden, the Netherlands, ²Experimental Medicine, Biogen Idec, Cambridge, MA, USA, ³Netherlands Metabolomics Centre, Leiden, the Netherlands, ⁴Analytical Biochemical Laboratory BV, Assen, The Netherlands

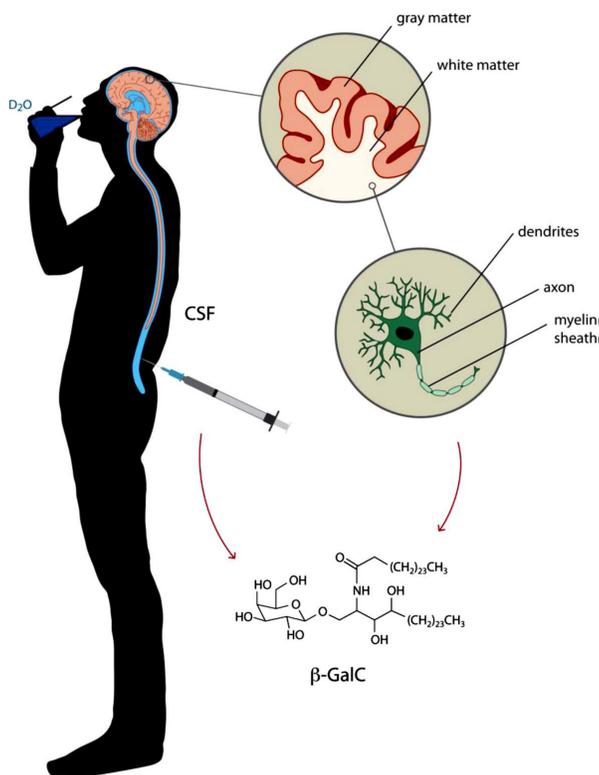
INTRODUCTION

Demyelinating diseases, such as multiple sclerosis (MS), are characterized by an increased breakdown of myelin with a subsequent failure of the remyelination process.

Enhancement of remyelination may improve recovery after an exacerbation¹. However, direct enhancement of remyelination can only be shown when myelin turnover rate can be quantified. The turnover rate of biomolecules can be determined by quantification of deuterium labeling after chronic administration of deuterated water (D₂O). Although the labeling of myelin cannot be determined directly in vivo, typical breakdown products or myelin precursors such as beta-galactosylceramide (BGalC) can be measured in cerebrospinal fluid (CSF)².

METHODS

- 6 healthy volunteers
- Daily 120mL 70% D₂O, 70 days
- 5 lumbar punctures (days 35, 70, 93, 167 and 548 or 714)
- LC/MS/MS System for BGalC analysis in CSF³
- BGalC turnover rate estimated using non-linear mixed effects modeling



RESULTS

Although a high deuterium fraction of body water was observed (up to 3.9%, see figure 1), the deuterium fraction measured in BGalC was markedly lower (up to 0.14%, see figure 2). The deuterium fraction in GalC remained relatively stable during the study period, in subjects 1,2,4 and 5 even 100 days after the last dose of D₂O. A two-compartment turnover model best characterized the deuteration of body water and BGalC. The differences in BGalC deuteration were explained by interindividual variability in body water turnover. **The estimated turnover rate of BGalC is 1150 (CI = 1077 – 1223) days.**

CONCLUSIONS

A slow rate-limiting biochemical step is suggested by the data and estimation of BGalC turnover rate. This is likely due to the production and/or degradation of myelin. The estimated BGalC turnover rate is a potential, quantitative biomarker for myelin kinetics.

Further research:

- Repeat study in MS patients, eventually with remyelinating compound
- This approach may be applicable for other CSF biomarkers

Deuterium fraction in body water: Predictions versus observation

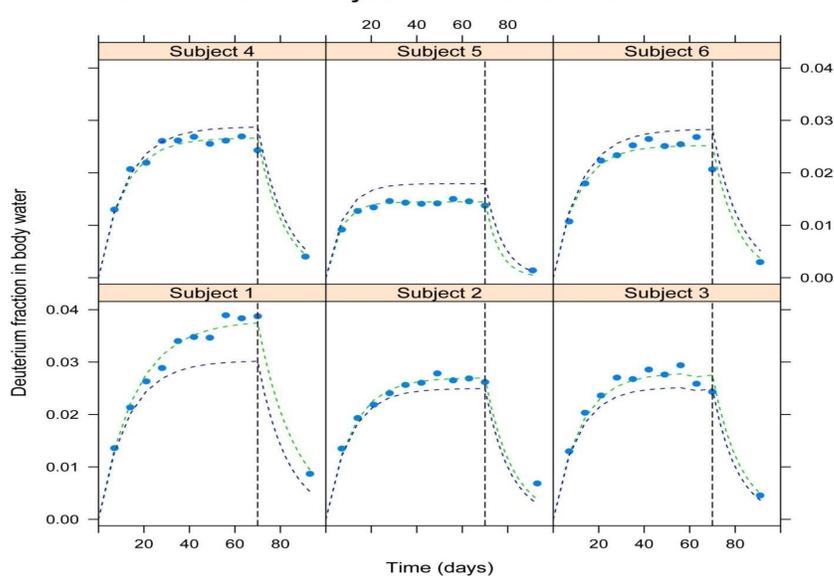


Figure 1: Body water enrichment. Shown are observations (closed blue circles), population predictions (dashed green line) and individual predictions (dashed blue line). The vertical dashed line is the end of the 70 day dosing period.

Deuterium fraction in BGalC: Predictions versus observation

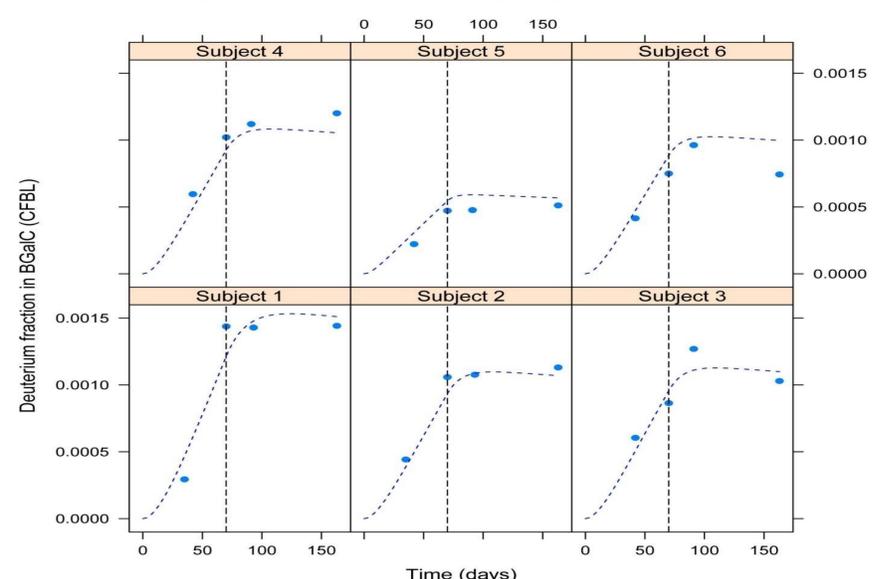


Figure 2: BGalC enrichment. Shown are observations (closed blue circles) and model predictions (dashed blue line). The vertical dashed line represents the end of the 70 day dosing period.

References: 1. Hartley, Altowaijri, Bourdette (2014) Remyelination and multiple sclerosis: therapeutic approaches and challenges. pp 484. 2. Quarles, Macklin, Morell (2006) Myelin Formation, Structure and Biochemistry. In: Basic Neurochemistry: Molecular, Cellular and Medical aspects pp 51-71. 3. Ando S, Tanaka Y, Toyoda Y, Kon K (2003) Turnover of myelin lipids in aging brain. Neurochem Res 28:5-13.

One or more authors report potential conflicts which are described in the program.

CHDR
Centre for Human Drug Research

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands
Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl