A mechanism for exchange between intraaxonal and extracellular water: Permeable nodes of Ranvier

M. Nilsson[1], H. Hagslätt[2,3], D. van Westen[2,3], R. Wirestam[1], F. Ståhlberg[1,3], and J. Lätt[1,2]
[1]Department of Medical Radiation Physics, Lund University, Lund, Sweden, [2]Center for Medical Imaging and Physiology, Lund University Hospital, Lund, Sweden,
[3]Department of Diagnostic Radiology, Lund University, Lund, Sweden

Introduction

Studies investigating the diffusion time dependence at high *b*-values often exclude the exchange between the intraaxonal and extracellular space [1]. However, inclusion of this exchange has been suggested to explain findings from diffusion MRI measurements with different diffusion times [2, 3]. So far plausible biophysical mechanisms for the exchange have been lacking; myelin sheaths around the axons are supposedly nearly impermeable and in addition have short T2-relaxation times. In this study, we demonstrate that water exchange occurring exclusively at the nodes of Ranvier could result in intraaxonal water exchange times τ_{ax} on the sub-second scale, depending on internodal distances and nodal permeability. Hence water exchange in white matter might be measurable using diffusion MRI and could be an important biomarker in neurological disease as well as in brain maturation.

Background

Nodes of Ranvier are gaps between the segments of myelin sheaths covering the axons. At the node, the axonal membrane is in direct contact with the extracellular space and the width w of the gap at the node is approximately 1 µm [4]. The distance between the nodes, i.e. the internodal length L, depends on the axon diameter d and the fibre type. In rat anterior medullary velum, the length varied between 100 and 400 µm [5], but it is much shorter in developing white matter [6].

Method

Monte Carlo simulations were performed in a three dimensional geometry mimicking myelin covered axons with nodes of Ranvier of width w, separated by an internodal segment of length L (Fig. 1). The three simulated compartments were the intraaxonal space, the myelin sheath and the extracellular space, shown in white, black and gray, respectively in Fig. 1. The inner diameter of the axon d, the extracellular volume fraction c_e, the physical diffusion coefficient D in all compartments and the nodal width w were held constant at d = 4 µm, c_e = 30%, D = 2.5 µm^2/ms and w = 1 µm. The time step in the simulations was 2.7 µs.

The intraaxonal exchange time τ_{ax} was investigated for exchange occurring exclusively at the nodes of Ranvier using 100 000 simulated particles, with intraaxonal particles allowed to leave their confinements, but not to reenter [3]. The exchange time was determined for different values of the membrane permeability P and different values of L. The effective permeability P_{eff} was calculated from τ_{ax} according to $P_{eff} = (\tau_{ax})^{-1} \cdot (V/A) \cdot (L/w)$, where V/A is the volume-to-surface ratio of the intraaxonal space.

Signal-versus-*b* curves were also simulated with diffusion encoding duration δ = 20 ms and diffusion time T_D = 50 and 150 ms. These simulations were performed with exchange exclusively at the nodes of Ranvier and, for comparison, also with assumed exchange along the complete axon due to permeable membranes with a corresponding permeability of $P_c = P\ (w/L)$. In this case, particles were distributed in the intraaxonal and extracellular spaces and exchange was allowed in both directions at the nodes.

Results

The intraaxonal exchange times were dependent on the internodal distance L (Fig. 2). For low values of P, the effective permeability P_{eff} was close to P, while P_{eff} was lower than P at high values of P, with increasing reductions for large L (Fig. 3). The diffusion time dependence of the simulated signal-versus-*b* curves was similar for diffusion simulated with exchange exclusively at the nodes of Ranvier compared with a correspondingly reduced permeability along the whole axon (Fig. 4).

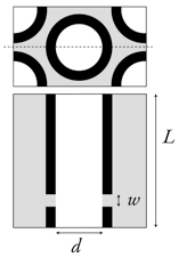

Fig. 1. Transverse and sagital segments of the 3D-simulation geometry. The dashed line represents the position of the sagital slice. Myelin is shown in black.

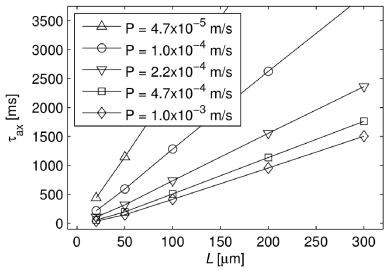

Fig. 2. The intraaxonal exchange time τ_{ax} as a function of the internodal distance L, for different nodal permeability P. Large L led to longer τ_{ax}, but in many cases τ_{ax} was on the sub-second scale. The selected values of P are within a biologically realistic range.

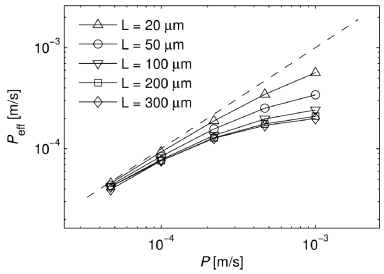

Fig. 3. The effective permeability P_{eff} versus the nodal permeability P. For high P, the effective permeability P_{eff} is reduced due to the large distance between the nodes. This means that for large L, P is less important than L for the obtained τ_{ax}.

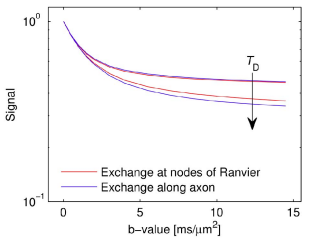

Fig. 4. For both T_D = 50 and 150 ms, very similar signal-versus-b curves were observed when comparing exchange at the nodes of Ranvier (red) or along the whole axon (blue), shown for τ_{ax} = 225 ms.

Discussion and conclusion

We suggest that axonal water exchange should be included in compartment models. The exchange can be modeled using the Kärger equations [2], which models the exchange as occurring along the complete axon. This modeling is sufficient, since signal-versus-*b* curves are similar for exchange occurring exclusively at the nodes of Ranvier and exchange along the total length of the axonal membrane (Fig. 4). If compartmental exchange is not included into the models, estimation of axonal density distribution may be biased, because thin axons (d < 4 µm) with short nodal distances (L < 100 µm) may show exchange times in the 10-400 ms range. Note that the permeability expected in biological membranes are within the range of nodal membrane permeabilites investigated [7]. In conclusion, exchange between the intra- and extracellular spaces occurring exclusively at the nodes of Ranvier offers a plausible mechanisms for axonal water exchange.

References [1] Barazany D, *et al*., Brain 2009:132(5):1210-1220 [2] Stanisz G, *et al*. MRM 1997:37(1):103-111 [3] Nilsson M, *et al*. MRI, 2009:27(2):176-187 [4] Hilderbrand C, *et al*. Prog. Neurobiol. 1993:40:319-384 [5] Butt *et al*., J Neurocytology. 1998:27:259-269. [6] Bjartmar C, Neurosci. Lett. 1996:216:85-88 [7] Benga G, Prog. Biophys. Molec. Biol. 1988:51:193-245.