Neurite Beading is Sufficient to Decrease the Apparent Diffusion Coefficient Following Ischemic Stroke

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Introduction

Within minutes of the onset of ischemic stroke, the apparent diffusion coefficient (ADC) dramatically decreases in the infarcted brain region[1]. However, although the ADC change is likely related to cell swelling, the precise biophysical mechanism remains elusive. Importantly, swelling of axons and dendrites, collectively known as neurites, causes a beaded morphology, the biophysics of which has been investigated in membrane tubes[2], in vitro[3], and in vivo[4]. We propose that swelling-induced neurite beading is sufficient to decrease ADC following ischemic stroke due to the restriction of water mobility caused by undulations of the cell membrane.

Methods

A geometrical model of beaded neurites was created with Matlab (**Fig. 1**) using a modified version of the contour described in Ref. 3. Surface area and length were conserved, and the average radius was free to vary to meet this condition. Geometries had an initial radius of 1 μm, infinite length, a free diffusion coefficient of 2.4×10^{-3}mm^2/s, and impermeable boundaries. Diffusion was simulated in the intracellular space using a random walk Monte Carlo routine implemented in the Camino toolkit[5] with 10,000 spins and 500 timepoints. Diffusion weighting was applied along three orthogonal axes using a b-value of 1000 s/mm^2 and diffusion gradient parameters of Δ=18 ms and δ=6 ms. Sciatic nerves were excised from six, 8 week old Wistar rats, ligated at each end, and subjected to tension sufficient to either straighten the nerves or impart a beaded axonal membrane[6]. Nerves were immediately fixed in 0° C Karnovsky's fixative. Fixed nerves were placed in a 7T Bruker vertical bore MRI and diffusion weighted spectroscopy was performed along the three orthogonal axes at b-values of 0-1000 s/mm^2 in 200 s/mm^2 increments and Δ=10 ms and δ=4 ms. A least squares fit to the equation $S_i = S_0 \bullet \exp(-b/D)$ was used to derive diffusion parallel ($ADC_{\parallel}$), diffusion perpendicular ($ADC_{\perp}$), mean diffusivity (MD), and fractional anisotropy (FA).

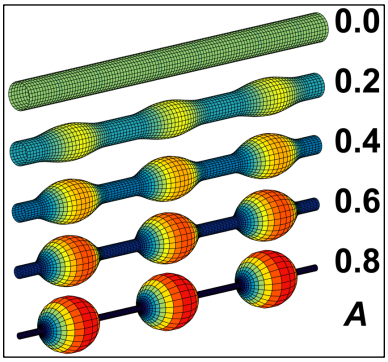

Figure 1. Biophysical model of beading as a function of beading amplitude (*A*).

Results and Discussion

The biophysical model of beading results in a smooth and continuous surface that encompasses a greater volume with increasing beading amplitudes while surface area and length remain constant (**Fig. 2**). This mimics the characteristics of beading neurites following acute changes in ionic balances such as those experienced following ischemic stroke. Diffusion parallel to the neurite was highly restricted with increased beading, whereas diffusion perpendicular to the neurite was largely unaffected (**Fig. 3**). Sciatic nerves were subjected to stretch-induced beading of the axonal membrane. The diffusion properties of these nerves demonstrated a significant decrease in the diffusion parallel to the axon, but no change perpendicular to it, resulting in a significant decrease in mean diffusivity and no change in anisotropy (**Fig. 4**).

Conclusion

A biophysical model of neurite beading is presented that is sufficient to decrease ADC solely due to cell membrane shape changes. The model is consistent with the known pathology as well as the diffusion changes measured in vivo following ischemic stroke.

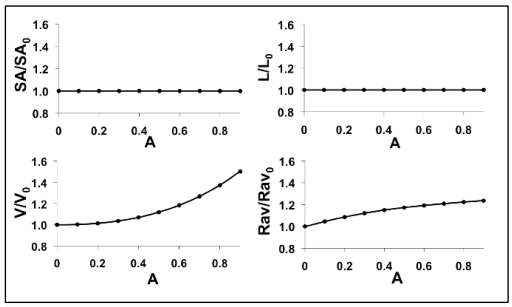

Figure 2. Normalized physical parameters of beaded neurites. The volume (V) encompassed by the neurite increased as a function of beading amplitude (A), whereas surface area (SA) and length (L) were held constant. The average radius (Rav) of the cylinder increased to accommodate the increased volume.

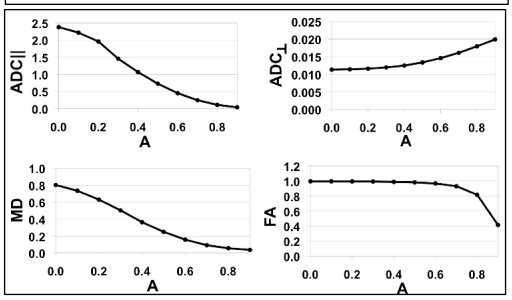

Figure 3. Simulated intracellular diffusion properties. Diffusion parallel to the neurite was highly restricted with increasing beading amplitude, whereas diffusion perpendicular to the neurite had only a minor increase. Consequently, the mean diffusivity dramatically decreased, but anisotropy was decreased only at the largest beading amplitudes.

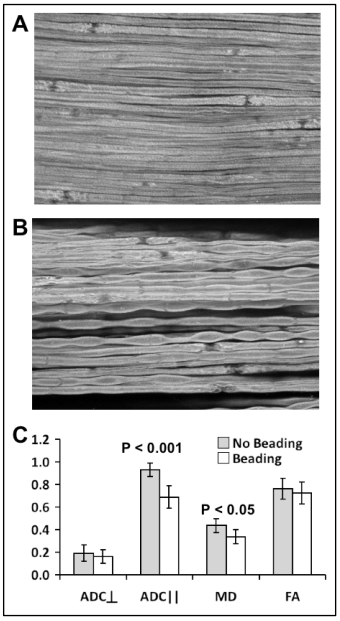

Figure 4. Diffusion in ex vivo beaded sciatic nerves. Compared to the unbeaded nerves (A), the beaded nerves (B) had a significant decrease in diffusion parallel to the neurite, whereas diffusion perpendicular to the neurite was not significantly different (C). This resulted in a decreased mean diffusivity but no change in anisotropy.

References [1]Mosley, et al. 1990. *AJNR*:11; [2]Bar-Ziv & Moses. 1994. *Phys Rev Lett*:73; [3]Markin, et al. 1999. *Biophys J*:76; [4]Murphy, et al. 2008. *J Neuroscience*:28; [5]Hall & Alexander. 2009. *IEEE Trans Med Imaging*; [6]Ochs, et al. 1994. *Neuroscience*:61.