Metabolic capacity of mammalian axons

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Brain is one of the body's most metabolically expensive tissues, and a large proportion of its energy budget (an estimated 35%) goes to restore ionic balances following action potentials [1]. Despite the importance of energy metabolism to neuronal computation, we know little about the metabolic cost of spiking. Metabolic capacity can be estimated by the fraction of cytoplasm occupied by mitochondria. Thus to study the metabolic demand of spike propagation we measured the mitochondrial content of retinal ganglion cell axons.

Analyzing electron micrographs, we reconstructed the distribution and volume of mitochondria within the axons, both in the unmyelinated segments (in retina) and in the myelinated segments (in optic nerve). Conventional wisdom states that the main energy cost lies in restoring the Na^+/K^+ balance following action potentials. It follows that: (i) total mitochondrial volume should be proportional to axonal membrane capacitance, therefore membrane surface area; (ii) since myelination reduces membrane capacitance by several orders of magnitude, mitochondrial volume in the myelinated axon segment should thus be correspondingly smaller than in the unmyelinated segment; (iii) mitochondria might be expected to accumulate at or near the nodes of Ranvier, as they do at other regions of high ion pumping activity (e.g., the photoreceptor inner segment). Instead we found: (i) mitochondrial volume was a roughly constant fraction of axoplasmic volume (3.4 for unmyelinated and 1.6% for myelinated axons); (ii) myelination reduced mitochondrial volume by a factor of only ~2.5; (iii) mitochondria, which were 3 ±2.3µm (mean ± SD) long did not accumulate near the nodes of Ranvier; instead they distributed randomly along the length of the axon, with an estimated mean separation between mitochondrion centers of 3.2 µm, and an average distance between mitochondria and nodal membrane of 0.4 µm.

The finding that mitochondrial volume scales with axon volume and not with axonal membrane surface area might be explained if ganglion cell firing rates scaled linearly with axon diameter, giving a power requirement that would scale as (surface area) x (diameter). Simultaneous measurements of ganglion cell firing rate and axon volume are not available. However, we do know that the cell type with the thinnest axons are 'local-edge', with mean firing rates to natural scenes of ~4 spikes/s and that the cell type with the thickest axons are 'brisk-transient' with mean firing rates of ~8 spikes/sec [2]. More generally the hypothesis predicts a match between the distribution of axon diameters and the distribution of firing rates, and this is roughly what we find. It is less clear why a cell with a higher firing rate should need a larger axon. The conventional wisdom is that by achieving a higher conduction velocity, the conduction time to the brain is shorter. Yet, the distribution of fiber diameters is conserved from mouse to man, despite a 10-fold increase in conduction distance. Alternatively, the higher firing rates, which carry more information [2], might require a larger terminal arbor with more vesicle release sites to transfer the information; thus we hypothesize that a larger axon is needed to provide greater capacity for axonal transport to supply the larger terminal arbors. This is consistent with findings in retina that neurons carrying more information have more active zones and thicker axons [3]. The reason why myelination saves so little remains unanswered.

References

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