An Estimate of the ATP Requirement of Human Retinal Ganglion Cells

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Abstract

Retinal ganglion cells (RGCs) are particularly susceptible to an impaired energy supply. Using human data on retinal oxygen consumption and basic energy metabolism stoichiometry, we estimate that the RGCs require at least 4.7×10^8 ATP molecules per second to maintain visual perception.

Retinal ganglion cells (RGCs) are the output neuron of the retina, encoding complex, digitized, information about the visual environment in the spatio-temporal pattern of their action potentials. They have a number of subtypes, categorized morphologically and functionally, and total approximately 1.1 million in the human retina.[1] Evolutionary pressures to optimize vision and neocortex size in humans have resulted in a limited retinal vasculature, unmyelinated RGC axons within the retina, and a relatively long distance between the RGC somata and their central synapses. These factors make the RGCs particularly susceptible to energy insufficiency and resulting neurodegeneration in conditions such as glaucoma.

Using data from two classic human experiments and some basic metabolic stoichiometry, we have derived an estimate for the lower limit of the adenosine triphosphate (ATP) required by RGCs to maintain visually significant action potentials. In 1951, Werner Noell, reported on the "site of asphyxial block in mammalian retinae". One of the mammals was himself. He concluded that, in the human retina, the RGCs were the element most vulnerable to anoxia and that it was the loss of their spike potentials that resulted in anoxia-induced "blackout". In 1968, Banks Anderson Jr. recorded the time to blackout in healthy volunteers breathing variable concentrations of oxygen.[2] The subjects were required to report when an 8 x 88 mm vertical black line at a distance of 1.8 m completely disappeared. From these data, he estimated that the oxygen requirement of the retina was approximately 7 ml/min/100 ml tissue. Taken together, we conclude that the RGCs require at least this rate of oxygen to maintain vision.

The derivation of the ATP required per RGC per second is calculated as follows:

Firstly, the retinal mass is required. To our knowledge, the average mass of the wet human retina has never been reported. We estimated the retinal mass by multiplying its area (~1100 mm^2) by its average thickness (~250 μm) by its density (~1000 kg/m^3), and then using Anderson's value of 7 ml/min/100 ml tissue to calculate the total retinal oxygen consumption: (0.007/60) x (retina mass/0.1) = 3.208 x 10^{-7} L/s. From the ideal gas law, we can calculate the

number of moles of oxygen in this volume at standard pressure (1 atm) and body temperature (310 K). We can then calculate the number of molecules of O_2 by multiplying the number of moles by Avogadro's constant. The complete aerobic oxidation of glucose has the following stoichiometry: $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$. The exact number of ATP molecules produced per mole of glucose is not consistent because it is powered by the proton motive force and is never an exact integer but is approximately 30 moles of ATP per 6 moles of oxygen. We calculate that the retina produces (and demands) approximately 3.8×10^{16} molecules of ATP per second. However, each neuron is unlikely to receive an equal share. In particular, the photoreceptors, although having inner segments packed with mitochondria, are known to exhibit aerobic glycolysis, generating a significant fraction of their ATP without consuming O_2. Based on data from Winkler's retinal metabolism experiments in rats,[3] we estimate that approximately 40% of the photoreceptors' ATP requirement does not consume O_2. Similarly, our own data and evidence of the oxygen tension at different layers of the retina indicates that the bipolar and Müller cells consume relatively small amounts of O_2.[4] In fact, elegant experiments by Yu *et al*. indicate that the greatest change in oxygen flux occurs in the inner plexiform layer, potentially representing the oxygen consumption of RGC synapses.[4] This is consistent with the large number of mitochondria in this zone,[5] and the relatively large ATP requirement of dendrites.[5] These experiments provide information about oxygen flux, but are unable to provide an absolute value for O_2 consumption in the ganglion cell layer.

Based on modern estimates of retinal cell numbers in the human[6, 7] and mouse retina,[8] we estimate that the total number of O_2 consuming cells in the human retina is ~ 125 million (Osterberg's frequently cited estimated rod count of 123 million was from a single human cadaveric eye, and suffered from technical inaccuracies.[9]) Of these, approximately 1100000 are RGCs.[1] If the RGCs receive an equal share, then each RGC requires 4.68×10^8 ATP molecules per second to prevent complete loss of vision. This is about 5-fold greater than the

requirement of mammalian photoreceptors in darkness[10], but about 10-fold less than the requirement of cortical neurons, estimated from metabolic neuroimaging in conscious healthy volunteers.[11] However, the value of ~ 4.7 x 10^8 ATP molecules per second for RGCs is similar to the requirement of unmyelinated hippocampal axons (mossy fibers) to maintain action potentials.[12] Hence, it seems reasonable to interpret this estimate as a lower limit to barely maintain some function. Arguably, given that central vision is the last region to blackout, the calculations could be performed for macula RGCs only; however, it is difficult to extrapolate to this extent from the Andersson experiment. It is likely that the energy requirements to maintain normal vision are considerably greater.

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