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Retinal ganglion cells: Energetics, compartmentation, axonal transport, cytoskeletons and vulnerability

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ABSTRACT

Retinal ganglion cells (RGCs) are specialized projection neurons that relay an immense amount of visual information from the retina to the brain. RGC signal inputs are collected by dendrites and output is distributed from the cell body via very thin (0.5–1 μm) and long (~50 mm) axons. The RGC cell body is larger than other retinal neurons, but is still only a very small fraction (one ten thousandths) of the length and total surface area of the axon. The total distance traversed by RGCs extends from the retina, starting from synapses with bipolar and amacrine cells, to the brain, to synapses with neurons in the lateral geniculate nucleus.

This review will focus on the energy demands of RGCs and the relevant tissues that surround them. RGC survival and function unexceptionally depends upon free energy, predominantly adenosine triphosphate (ATP). RGC energy metabolism is vastly different when compared to that of the photoreceptors.

Each subcellular component of the RGC is remarkably different in terms of structure, function and extracellular environment. The energy demands and distribution of each component are also distinct as evidenced by the uneven distribution of mitochondria and ATP within the RGC – signifying the presence of intracellular energy gradients. In this review we will describe RGCs as having four subcellular components, (1) Dendrites, (2) Cell body, (3) Non-myelinated axon, including intraocular and optic nerve head portions, and (4) Myelinated axon, including the intra-orbital and intracranial portions.

We will also describe how RGCs integrate information from each subcellular component in order achieve intracellular homeostatic stability as well as respond to perturbations in the extracellular environment. The possible cellular mechanisms such as axonal transport and axonal cytoskeleton proteins that are involved in maintaining RGC energy homeostasis during normal and disease conditions will also be discussed in depth. The emphasis of this review will be on energetic mechanisms within RGC components that have the most relevance to clinical ophthalmology.

Contents

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1. Introduction

All biochemical reactions involve energy exchange. A large quantity of internal free energy is therefore required for cell survival and function (Alberts B et al., 2002). The key forms of intracellular free energy are nucleotide triphosphates, such as ATP. ATP is produced by a series of chemical reactions and synthesized either by oxidative phosphorylation in mitochondria (approximately 90% of total) or by glycolysis in the cytosol. Roughly 10^9 molecules of ATP are present in a single cell at any instant and, in many cells, all of this ATP is used and replaced every 1–2 min (Alberts B et al., 2002).

It is estimated that ~20% of total oxygen consumption in the human body occurs in the brain which constitutes only ~2% of total body weight (Coyle and Puttfarcken, 1993). Arguably, the energy demands of retinal tissue are even greater than brain tissue, with estimates of oxygen consumption per tissue weight in the retina being one of the highest in the human body (Ames and Li, 1992).

RGCs are specialized projection neurons that convey visual information from the retina to the brain. 90% of all sensory signals that are integrated in the brain are of visual origin and almost a third of the cortical surface is devoted to visual processing (Chalupa and Werner, 2004). RGCs have a large cell body, relative to other retinal neurons, and these cell bodies are located along the inner margin of the retina, in the retinal ganglion cell layer. The biogenesis site of all organelles and cytoplasm is the cell body and for this reason the functional activity and survival of RGC axons and dendrites are dependent upon the RGC soma (Munemasa and Kitaoka, 2012).

The histological section shown in Fig. 1 is taken from the parafoveal region of a monkey retina where the RGC bodies are smaller than in the peripheral retina. The RGC cell body has a rich cytoplasm. Like most neurons, RGCs are polarized into dendritic and axonal compartments that are connected at the cell body. The molecular differences within a neuron that result in structural polarisation are also responsible for some degree of functional polarisation. In the RGC, signal inputs are collected by the dendrites and a pulse-coded signal is transmitted from the cell body via the axon. RGC dendrites extend into the inner plexiform layer (IPL), a neuropil located on the outer side of the RGC layer. Abundant synaptic contacts are located in the IPL. RGCs receive inputs from bipolar cells, which convey signals from photoreceptors to the IPL, and from amacrine cells that branch in the IPL (Fig. 1). There are approximately 20–30 subtypes of amacrine cells that are structurally diverse with respect to the distribution of their processes.

The visual stimulus is unique as it undergoes a tremendous amount of processing within retinal layers, encompassing the spatial and temporal properties of the light stimulus, prior to transmission by RGC axons to the brain (Hogan et al., 1971). More than 1 million RGC axons form the optic nerve, a vital structure that acts as a conduit between the retina and the brain. Most nerve axons are 0.5 μm or more in diameter and ~50 mm in length. It is worth noting that axon fibres, which serve as the primary signal conduit in neurons, are on average ~20,000 times larger than the cell body with respect to length and total surface area (Friede, 1963). The optic nerve contains 38% of all the afferent fibres contained in cranial nerves (Hogan et al., 1971).