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Review article

Rod metabolic demand drives progression in retinopathies

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ABSTRACT

Various factors are thought to cause the development and progression of disease in macular degeneration, diabetic retinopathy, and retinitis pigmentosa. Some of the deleterious processes include oxidative stress, hypoxia, metabolic derangement, genetics, and vasculopathy. In this review, we present a unified theory for the pathophysiology of several retinopathies based on the unique and intense metabolism of rod photoreceptors.

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1. Introduction

Rod photoreceptors consume more energy in darkness than in light.[1] Unlike most other neurons, rods do not fire action potentials. Rather, in darkness they exhibit a continuous depolarized state of the rod membrane potential that allows constant neurotransmitter release to activate second-order neurons in the visual pathway.[2] The "dark current" is maintained by cyclic-nucleotide-gated (CNG) channels that allow inward flow of cations, approximately 80% Na^+ and 15% Ca^{2+}. The Ca^{2+} influx is balanced by a Na^+/Ca^{2+}–K^+ exchanger that exchanges four Na^+ inward for one Ca^{2+} and one K^+ outward, and the large Na^+ influx is balanced by a Na^+/K^+ ATPase at the inner segment.[3] Rods consume up to four times as much adenosine triphosphate (ATP) in darkness as that in light to support the high energy demand of these transporters; one ATP is consumed per Ca^{2+} exported and one ATP is consumed per three Na^+ exported.[3] Photoexcitation closes the CNG channel, preventing influx of Na^+ and Ca^{2+} and causing hyperpolarization across the rod membrane, which reduces neurotransmitter release. For reviews of phototransduction, see the works of Yau and Hardie[3] and Fain et al.[4]

Briefly, in rod phototransduction, light activates rhodopsin, which activates the G protein transducin, which in turn activates phosphodiesterase, which hydrolyzes cyclic guanosine monophosphate (cGMP) to guanosine monophosphate (GMP).[5–9] Removal of cGMP from the CNG channel causes channel closure and prevents the influx of cations.[3,4]

The high energy demand for maintaining the "dark current" causes rods to consume the highest amount of energy among all cell types in the body.[10–12] A large amount of ATP and Nicotinamide adenine dinucleotide phosphate (NADPH) are needed for recovery of cGMP from photoexcitation and its resynthesis in darkness.[1] In darkness, to meet the ATP demands of ion transporters, rods use large amounts of O_2 and glucose that are metabolized by both glycolysis and oxidative phosphorylation (Fig. 1).[13,14] In light, however, consumption of O_2 by rods was shown to decrease by approximately 30% in macaques and approximately 50–70% in cats,[10–12] indicating a marked reduction in oxidative phosphorylation in light compared with that in darkness (Fig. 1). In light, there is increased anabolic activity[14]; mRNA levels are increased four to 10 times,[15,16] and outer segments appear to follow a circadian pattern, in which discs are shed more at the onset of light in a 12-hour light–dark cycle irrespective of whether the lights are turned on or not, which is accompanied by an increase in outer segment renewal,[17,18] presumably fueled by increased lipid and protein production.

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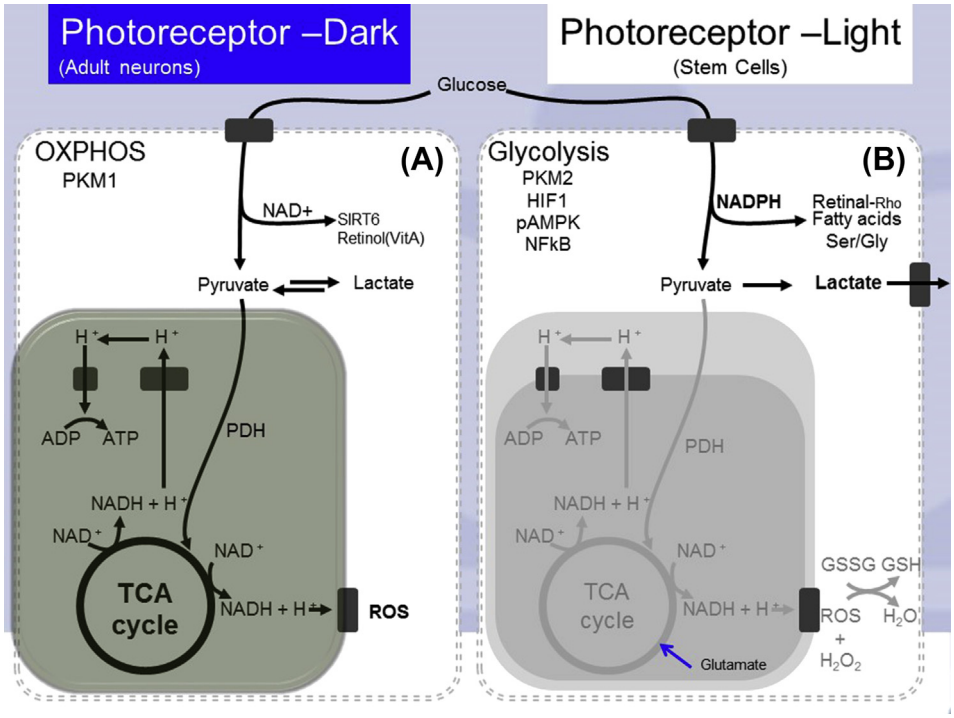

Fig. 1. (A) In darkness, photoreceptor metabolism is similar to adult neurons. Glucose is catabolized through glycolysis, the TCA cycle, and oxidative phosphorylation, generating NAD+ and a large amount of ATP along with ROS. (B) In light, photoreceptor metabolism is similar to that of stem cells. Glucose undergoes glycolysis to form pyruvate, which is not further catabolized by the TCA cycle but is metabolized by the pentose phosphate pathway, generating several molecules of NADPH. NADPH is used for anabolic production of fatty acids, proteins, nucleic acids, and 11-cis retinal. ADP = adenosine diphosphate; ATP = adenosine triphosphate; HIF1 = hypoxia inducible factor 1; NFκB = nuclear factor kappa beta; PKM = pyruvate kinase muscle isozyme; ROS = reactive oxygen species; TCA = tricarboxylic acid; NADH = nicotinamide adenine dinucleotide (reduced); NAD^+ = nicotinamide adenine dinucleotide (oxidized); PDH = pyruvate dehydrogenase; pAMPK = phosphorylated adenosine monophosphate activated protein kinase; NADPH = nicotinamide adenine dinucleotide phosphate; Ser = serine; Gly = glycine; GSSG = glutathione disulfide; GSH = glutathione.

2. Dark-adapted rod metabolism and the Warburg effect

The anabolic state of light-adapted rods is similar to the Warburg effect seen in cancer cells and stem cells, in which aerobic glycolysis is the exclusive catabolic process used to produce massive amounts of biomolecules for cell growth and division.[19,20] Conversely, dark-adapted rods exhibit glycolysis as well as oxidative phosphorylation, which, similar to conventional neuronal metabolism, consumes large amounts of glucose and O_2.[21] Much of the understanding of the Warburg effect can potentially be applied to rod photoreceptors in light adaptation. The shift from oxidative phosphorylation to glycolysis allows for the production of two NADPH molecules per glucose molecule via the pentose phosphate pathway, which fuels the anabolic processes of the cell, and synthesis of amino acids, nucleic acids, lipids, and carbohydrates.[22]

3. Cellular control of metabolism via hypoxia inducible factor 1 and SIRT6

Recently, new details of the molecular basis for the switch from aerobic respiration to aerobic glycolysis have been uncovered. It has long been known that a state of hypoxia or low nutrients induces cells to use glycolysis alone, rather than continuing catabolism through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. This switch to glycolysis is eponymously referred to as the "Pasteur effect." Recently, some molecular details have been uncovered. The low-oxygen sensing transcription factor, hypoxia inducible factor 1 (HIF1), was shown to activate transcription of genes, the products of which inhibit the TCA cycle and promote glycolysis.[23,24] HIF1 drives anaerobic glycolysis and regulates cancer metabolism, and it has been a target for cancer therapy.[25,26] The histone deacetylase SIRT6, a member of the sirtuin family, has been shown to have the opposite effect of HIF1 on metabolism and to function as a tumor suppressor.[27,28] While SIRT6 and HIF1 have both been touted as possible cancer therapy targets, their role in retinal diseases has yet to be explored. We postulate that activation of HIF1 or inhibition of SIRT6 can cause rods to switch from oxidative phosphorylation to aerobic glycolysis, reducing cellular consumption of ATP and O_2 to promote survival by preventing ischemia and oxidative damage.

4. Rod energy demand drives retinal degenerative diseases

The high energy cost and O_2 demand of dark-adapted rod cells are the bases for a recently developed theory for the mechanism of age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinopathy of prematurity.[29] During dark adaptation, partial pressure of oxygen nears zero at the ellipsoid zone where the rod mitochondria reside, which was shown in cats, monkeys, and rats.[10,12,30] In low-oxygen settings, such as at a high elevation,[31] and in diseases such as polycythemia vera[32,33] and partial carotid occlusion,[34] loss of dark adaptation is one of the first symptoms to manifest, indicating the high sensitivity of rods to hypoxic insult. Because rods operate in a near hypoxic state, any reduction in the oxygenation of the retina causes release of hypoxic factors, notably vascular endothelial growth factor (VEGF), which leads to neovascularization of either the choroidal (in AMD) or the retinal (in retinopathy of prematurity and DR) vasculature.[29]

5. Rod metabolism in AMD

Early pathological changes observed in AMD are thickening of Bruch's membrane and deposition of subretinal drusen.[35] These

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