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Review

24S-hydroxycholesterol and cholesterol-24S-hydroxylase (CYP46A1) in the retina: from cholesterol homeostasis to pathophysiology of glaucoma

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ABSTRACT

Free cholesterol is the predominant form of cholesterol in the neural retina. The vertebrate neural retina exhibits its own capacity to synthesize cholesterol and meets its demand also by taking it from the circulation. Defects in cholesterol synthesis and trafficking in the neural retina has detrimental consequences on its structure and function, highlighting the crucial importance of maintaining cholesterol homeostasis in the retina. Our purpose was to give a review on the functioning of the retina, the role of cholesterol and cholesterol metabolism therein, with special emphasis on cholesterol-24S-hydroxylase (CYP46A1). Similar to the brain, the retina expresses cholesterol-24S-hydroxylase (CYP46A1) and is enriched in its metabolic product, 24S-hydroxycholesterol. We recently published that one single nucleotide polymorphism in CYP46A1 gene, designated as rs754203, was a risk factor for glaucoma. Glaucoma is the second leading cause of blindness worldwide, affecting more than 60 million people. Glaucoma is characterized by the loss of retinal ganglion cells, which show high CYP46A1 expression. These data suggest the potential involvement of CYP46A1 and 24S-hydroxycholesterol in the pathophysiology of glaucoma.

Contents

1. Introduction

The retina covers the internal side of the ocular globe at its posterior pole. The retina is composed of the neurosensory retina and the retinal pigment epithelium (RPE). The retina is a sensitive target of aging. Age-related Macular Degeneration (AMD), diabetic retinopathy and glaucoma are the most prevalent retinal pathologies in aged Western populations. AMD is the leading cause of visual loss in developed countries (Fine et al., 2000). Glaucoma is the second blinding disease worldwide after cataract. More than 60 millions people suffer from glaucoma in the world in 2010, 80 millions are expected in 2020 (Quigley and Broman, 2006). Diabetic retinopathy is a major concern in the next decades, accounting the growing number of subjects with diabetes and that 30–40% of diabetic patients develop diabetic retinopathy.

The neurosensory retina is rich in lipids: 25% of the dry matter, partitioned between 90% phospholipids and 10% cholesterol (Bretillon et al., 2008b). Cholesterol is the main sterol in the vertebrate retina (Fliesler and Schroepfer, 1982). Cholesterol is exclusively present as the free form in the neurosensory retina (Bretillon et al., 2008b). Deposits of free cholesterol and cholesteryl esters at the basement of RPE are hallmarks of aging in humans, and

Abbreviations: AMD, age-related macular degeneration; DHA, docosahexaenoic acid; RGC, retinal ganglion cells; RPE, retinal pigment epithelium; SLOS, Smith-Lemli-Opitz syndrome.

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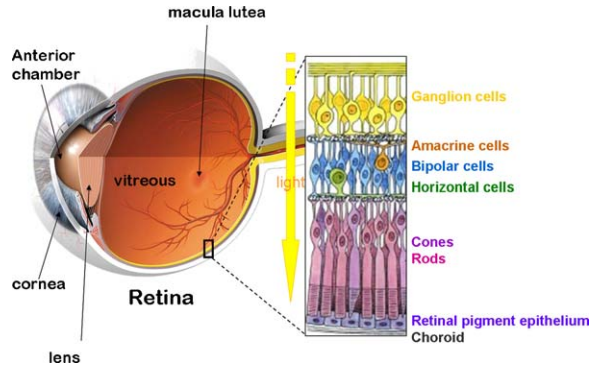

Fig. 1. Structural organization of the human eye and retina. The yellow arrow illustrates the way light enters the retina.

AMD (Curcio et al., 2010). The neurosensory retina belongs to the central nervous system. As such, it exhibits a specific physical and metabolic barrier which limits the entry of exogenous molecules and the export of endogenous ones.

In the present review, after a brief summary on the structure and function of the retina, we will highlight the main findings related to the putative role of cholesterol-24S-hydroxylase in the retina, and its age-related diseases.

2. Structure and function of the retina

The primary function of the retina is to convert light into an electrical signal which is transferred to the brain via the optic nerve. The neurosensory retina contains photosensitive cells, neurons and glial cells. Various types of neurons are present in the neurosensory retina: bipolar cells, ganglion cells, amacrine cells, horizontal cells. The architecture of the neurosensory retina is reverse to the way light enters. Indeed, cones and rods which are the light-sensitive cells are located at the most external side of the neurosensory retina, at the vicinity of the RPE (Fig. 1). The coding function of the retina is dependent not only to photoreceptors but also to neurons, glial cells and RPE which amplify the signal. Rods represent the prominent population of photoreceptors compared to cones, even in most diurnal animal species (Masland, 2001). The structural organization of photoreceptors and neurons in the retina is unique. The signal emerges from rods and cones independently, is transmitted to bipolar cells, and converges to ganglion cells. On the contrary to the cone pathway which involves a one-to-one association of cone-bipolar cell-ganglion cell, the rod system is much more convergent since the signal from many rods is pooled to generate a signal in one ganglion cells. About 100 millions of cones and rods and 1 million of ganglion cells are present in the retina. This relationship between photoreceptors, bipolar cells and ganglion cells maximize the response to light, especially in rods. The ability of photoreceptors to convert light photons into an electrical signal is due to the presence of a photopigment (opsin in cones, rhodopsin in rods) in their outer segments. The outer segment of a photoreceptor consists in a stack of disk membranes that are synthesized in the proximal portion of the outer segment and shed at its apical side. Rhodopsin is a G-protein coupled receptor which is present in the outer segments. Absorption of photon by rhodopsin yields conformational movements of rhodopsin that result in activation of the G-protein and biological response. The lipid environment of rhodopsin is a key effector of these changes (Brown et al., 2010). Docosahexaenoic acid (DHA) is a long chain polyunsaturated fatty acid from the omega 3 series. It is present at high levels in the neurosensory retina: about 15% in the whole human retina (Bretillon et al., 2008b), and accounts for 50% of the fatty acids in the outer segments of photoreceptors (Fliesler and Anderson, 1983). DHA improves the kinetics of the photocycle by creating specific intermolecular associations with rhodopsin. On the contrary, despite no direct specific interactions, cholesterol stabilizes rhodopsin and impairs its activation (Grossfield et al., 2006). Electroretinography is a suitable method to monitor the capacity of the retina to respond to light stimulus. The retina of animals reared under a diet deficient in omega 3 fatty acids is depleted in DHA, and shows a reduced electroretinographic response (Neuringer et al., 1986). The consequences of cholesterol deficiency on retinal function are far less well known than for DHA. Smith-Lemli-Opitz syndrome (SLOS) is a congenital metabolic disease which is characterized by the biochemical defect in the conversion of 7-dehydrocholesterol to cholesterol. The rodent model of SLOS shows a 2-fold reduction of the sensitivity and maximum amplitude response of rods to light stimulation, compared to control animals (Fliesler et al., 2004). It remains much more difficult to evaluate the situation in humans, since electroretinographic data in humans have been collected in patients treated by long term dietary supplementation with cholesterol starting at young ages. Nevertheless and despite this limitation, reduced saturated response amplitude of rods has been reported in SLOS patients (Garry et al., 2010). At the opposite of cholesterol depletion in SLOS, Niemann-Pick type C disease is characterized by cholesterol accumulation in neurons of the brain (Paul et al., 2004). Niemann-Pick type C disease is a rare autosomal recessive disorder characterized by the impairment of the endosomal–lysosomal pathway, leading to excessive storage of lysosomes. The mouse model of Niemann-Pick type C deficiency showed age-dependent altered electroretinographic response, and neurodegeneration (Claudepierre et al., 2010).

3. The metabolism of cholesterol in the retina

Cholesterol is exclusively present as free form in the neurosensory retina (Bretillon et al., 2008b), and distributed in all cell layers (Bretillon et al., 2008a). Cholesterol in the neuroretina originates from *in situ* synthesis and extra-retinal sources. The relative contribution of cholesterol coming from the circulation and local biosynthesis remains unknown. The capacity of the retina to synthesize cholesterol has been suggested from studies using radiolabelled precursors of cholesterol. RPE, Müller cells and rods express HMGcoA reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway (Fliesler and Bretillon, 2010). Lipoproteins, i.e., LDL and HDL, are the circulating carriers of free cholesterol and cholesteryl esters. RPE creates the blood-retinal barrier at the basement of the neurosensory retina. Tight junctions between RPE cells limit the intercellular movements of molecules to water and small molecules. RPE cells express various lipoprotein and scavenger receptors which can promote the recognition of cholesterol-rich lipoprotein and enhance the entry of cholesterol in the neurosensory retina (Fliesler and Bretillon, 2010). Indeed, Tserentsoodol et al. (2006) showed that cholesterol bound to LDL can reach the RPE and enter the neurosensory retina. As mentioned above, Müller cells express HMGcoA reductase. Glia is also known to support neurons in the formation and maintenance of synapses (Pfrieger, 2010) in which the role cholesterol is crucial (Pfrieger, 2003). Therefore and altogether these data suggest that glial Müller cells may also contribute to deliver cholesterol to neurons.

As illustrated from the consequences for the retina of cholesterol accumulation in the npc1$^{-/-}$ murine model of SLOS (Claudepierre et al., 2010), the export of cholesterol is mandatory to maintain the balance with cholesterol import and *in situ* biosynthesis. Both the neurosensory retina and RPE cells express proteins which participate to cholesterol export in other tissues than the retina, such as ABCA1, apoE, ApoA1 or SR-BI (Fliesler and Bretillon, 2010). The role and activity of these proteins in the retina remains to be fully defined. RPE cells have the capacity to synthesize lipoprotein-like