Overview

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Anatomy and Physiology of the Eye

Vision is our dominant sense. The eyes, specialized for the detection of light, are our most important sensory organs, providing approximately 70–80 % of our total sensory information. The optical apparatus projects an image of our environment onto the back of the eye covered by the retina. The retina is a neuronal tissue originating from the brain during embryonic development and is, thus, a true part of the central nervous system. The retina is a well-layered, appr. 200 µm thick tissue and can be divided into an outer part that harbors the light-sensitive cells – the rod and cone photoreceptor cells – and an inner part that comprises a neuronal network [1]. This network performs the first steps of information processing before the signal is relayed by the retinal ganglion cells to the brain via the optic nerve. A human retina harbors around 120 million rod and 6 million cone photoreceptor cells. Rods are highly sensitive, can respond to single light quanta, and provide vision during night and at twilight. Cones are less sensitive and provide color vision during daylight. Behind the retina, two more layers are located: the retinal pigment epithelium (RPE) and the choroid (see Fig. 1), a dense network of blood capillaries, which provides nutrients and oxygen to the photoreceptors. Both are separated by Bruch's membrane, an elastin- and collagen-rich structure [2].

Due to its function, the eye has to cope with special problems. Retinal cells are the only neurons exposed to light. Bright illumination can result in the generation of free radicals that damage the retinal cells (see below). As photoreceptors (like most other central neurons) cannot be replaced, the eye has developed several mechanisms of protection. The optical apparatus absorbs high-energy ultraviolet light, which would otherwise damage the retina [3]. Moreover, in the center of the retina, protective pigments are embedded that absorb light of short wavelengths, giving this area a yellowish appearance, called *macula lutea* (Latin: yellow spot) or briefly macula (Fig. 1a). Finally, the light-sensitive segments of the rod and cone photoreceptors are continuously renewed.

The eyeball is well protected in a cavity of the skull called orbit. The frontal part of the human eye can be covered by the eyelids. The surface of the eye is moisturized by tears produced by the lacrimal gland (situated in the upper outer part of the orbit). Tears are drained by the lacrimal puncta in the inner corner of the eyelids via the lacrimal sac into the nose (see chapter "Glaucoma"). Most of the eyeball is covered by the tough white sclera (Fig. 1a). In the front, the sclera changes over to the transparent cornea, the first and most refractive part of the optical apparatus. The iris is the colored part of the eye. It is a pigmented muscle tissue situated between the

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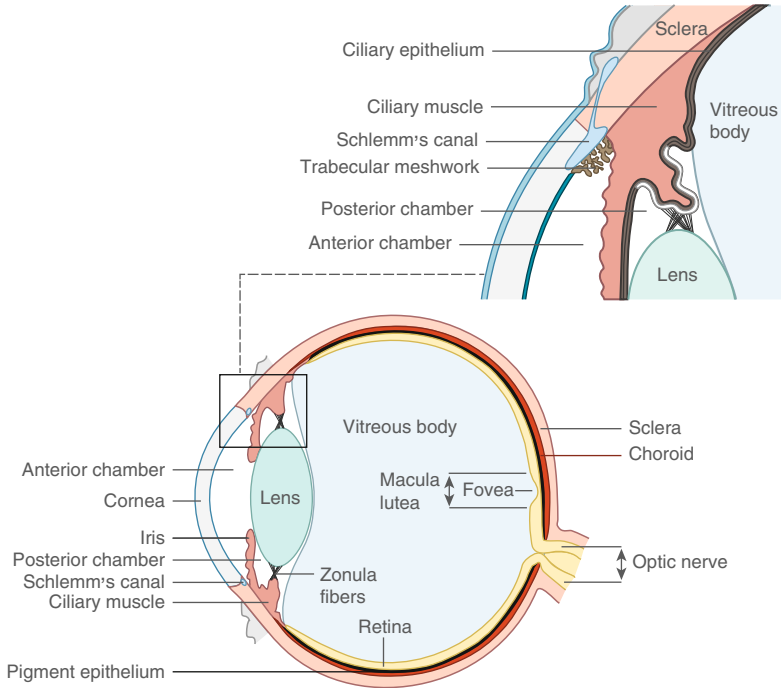

Fig. 1 Schematic cross section of an eye. The different layers perform important tasks: the choroid is a layer of blood vessels important for photoreceptor supply. The retina is a neuronal tissue comprising the photoreceptor cells, a network of neurons, and the retinal ganglion cells as output neurons that relay the information to the brain; it also contains the macula lutea with the fovea, the central part of the retina with the highest visual acuity. The retinal pigment epithelium, a monolayer of pigmented cells that forms part of the blood-retinal barrier, is involved in the regeneration of the photopigment and the phagocytosis of the photoreceptors' outer segments. The vitreous body is a jellylike transparent substance that maintains the eye in its spherical shape. Inset: Structures responsible for the control of aqueous humor. The ciliary epithelium secrets aqueous humor into the posterior chamber. The trabecular meshwork is a spongy tissue, which drains the aqueous humor from the anterior chamber together with Schlemm's canal

cornea and lens. Depending on the brightness of ambient light, the iris can contract or expand, thus changing the diameter of the pupil and controlling the amount of light falling into the eye. The lens is suspended by the zonula fibers attached to the ciliary muscles. Humans can adjust their focus to different viewing distances by contracting the ciliary muscles, which ultimately leads to changes in the shape of the lens. For their function, the cornea and lens must be transparent and, therefore, devoid of blood vessels. They are nourished by diffusion from the aqueous humor, a transparent, jellylike fluid located in the anterior and posterior chamber of the eye. The compartment between the lens and retina is filled with the jellylike vitreous body. The pressure of both aqueous and vitreous humor, the so-called intraocular pressure, is slightly elevated, keeping the eyeball spherical.

Metabolic and Molecular Pathways and Processes in the Eye

Production of Aqueous Humor

The aqueous humor is secreted into the posterior chamber of the eye by a part of the ciliary epithelium situated close to the region where the zonula fibers are attached (Fig. 1b). The composition of aqueous humor is relatively similar to blood plasma.

However, its protein concentration is low (less than 1 %), whereas ascorbate is up to 50 times higher than in blood plasma. Oxygen is derived

by diffusion from the cornea and from the vasculature of the iris [4]. The aqueous humor flows from the posterior chamber through the pupil into the anterior chamber (Fig. 1b) and drains away at the angle between the cornea and iris, where it passes through a porous tissue – the trabecular meshwork – into a collecting channel (Schlemm's canal), which empties into veins and thus into the bloodstream. In the healthy eye, the delicate balance between aqueous fluid production, circulation, and drainage must be maintained in order to keep the intraocular pressure at a constant level. Slow drainage of aqueous humor or overproduction may lead to an increase in intraocular pressure that can result in the death of retinal ganglion cells – a disease called glaucoma (see chapter "Glaucoma").

Retinal Metabolism

The retina is inverse, i.e., before light reaches the photoreceptors, it has to pervade the different retinal layers: three layers of somata (termed ganglion cell layer, inner nuclear layer, and outer nuclear layer), separated by two synaptic layers (i.e., inner and outer plexiform layer). The ganglion cells are the output neurons of the retina. Their axons form the optic nerve (Fig. 1a). As all neurons, retinal cells conduct information by generating electrical signals at their plasma membrane (see chapter "Overview" under part "Brain"). Inside the cell, there is a high concentration of K^+ ions and large polyanions (such as proteins and nucleic acids), while outside the Na^+ ion concentration is high resulting in a resting membrane potential of −70 mV.

Photoreceptor cells can be divided into two compartments (Fig. 2a). The inner compartment comprises the cell body, the axon with the synaptic region, as well as the biochemical machinery with the mitochondria and ribosomes for routine cell metabolism. The outer segment harbors all proteins to absorb light, to amplify the signal, and to generate an electrical signal in response to light.

Rod outer segments are effective light catchers. The outer segment of a human rod contains a stack of up to 800 flat, hollow membrane compartments, called discs (Fig. 2b). The latter contain a high concentration of the photopigment rhodopsin in their membranes (Fig. 2c). Altogether 50–150 million rhodopsin molecules are found within a photoreceptor cell. Rhodopsin belongs to the family of G-protein-coupled receptors (see below). It consists of a protein part (the opsin) and a light-absorbing cofactor, the aldehyde form of vitamin A, retinal (Fig. 2c, d).

Retinal can exist in two different conformations. The folded 11-*cis*-retinal is covalently bound within the opsin molecule (Fig. 2c). Absorption of a light quantum causes 11-*cis*-retinal to switch to the elongated all-*trans*-retinal (Fig. 2d), inducing a conformational change in the rhodopsin molecule. This conformational change activates the G-protein transducin, which in turn activates phosphodiesterase 6 (PDE6). The latter hydrolyzes cGMP, which acts as a signal transducer, amplifier, and molecular switch. In the dark, due to an elevated cGMP concentration, cGMP-dependent ion channels (called cyclic nucleotide-gated ion channels) in the outer segments are open, leading to an influx of Na^+ and Ca^{2+}, depolarization of the membrane potential, and transmitter release. Upon illumination and cGMP hydrolysis via PDE6, cGMP-dependent ion channels close. As fewer Na^+ and Ca^{2+} enter the cell, the membrane potential becomes more negative. Thus, during illumination, the cells are more hyperpolarized, and fewer transmitter molecules are released from the synapse. This kind of membrane potential modulation, also termed graded potentials, controls the activity of photoreceptor cells, like that of most retinal cells. Graded potentials induce variations in the site of membrane potential in contrast to the "all-or-nothing" action potentials. To shut off the signaling cascade, rhodopsin becomes phosphorylated [5] and then sealed by arrestin, which ultimately stops the interaction with transducin.

The photoreceptor information is relayed synaptically via the bipolar cells to the ganglion cells. Along this path, lateral neuronal interactions and feedback loops are provided by horizontal cells in the outer and by amacrine cells in the inner plexiform layer. As retinal output neurons, ganglion cells communicate via action potentials – short

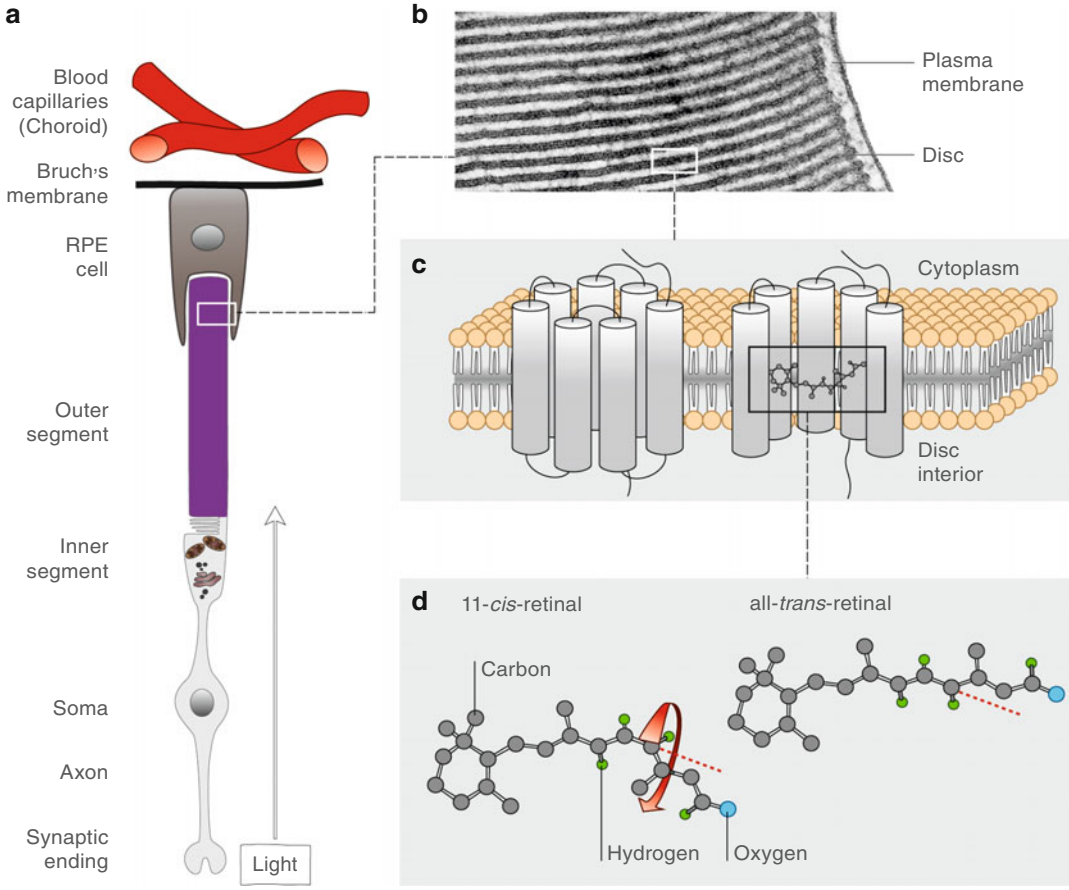

Fig. 2 Rod photoreceptor and rhodopsin. (**a**) Schematic overview of a rod photoreceptor and its surrounding layers. The blood capillaries of the choroid provide nourishment and oxygen to the photoreceptors. The retinal pigment epithelium (*RPE*) cells fulfill many functions (e.g., retinal metabolism and blood-retinal barrier). Note that the center of the eye is towards the bottom. The outer segments of the photoreceptor cells contain light-absorbing discs. The inner segments contain cell body and normal metabolic machinery. (**b**) Shows an electron micrograph of the region indicated in (**a**), showing an outer segment of a photoreceptor cell with its membranous discs. (**c**) Schematic of a disc membrane harboring the light-sensitive pigment rhodopsin, a G-protein-coupled receptor with seven transmembrane helices (*left*). Two helices are removed to reveal the retinal-binding pocket (*right*). (**d**) Chemical structure of free 11-*cis*- and all-*trans*-retinal. Light converts 11-*cis*-retinal into all-*trans*-retinal

(1–2 ms) stereotyped changes in membrane potential that propagate in an all-or-none fashion along the axons of neurons (chapter "Overview" under part "Brain").

The physiology of photoreceptors is extraordinary in the sense that a large ionic current in the dark is switched off in the light. Therefore, the energy consumption of the retina is four times higher in the dark than during illumination [6]. In the dark, about 50 % of the energy is used by the Na^+/K^+-ATPase to pump out excess Na^+ that enter the photoreceptors through open cGMP-dependent ion channels in the outer segment [7]. As during illumination the ion flux into the photoreceptor outer segment decreases, energy consumption by the Na^+/K^+-ATPase drops. However, the energy expenditure for the subsequent phosphorylation of rhodopsin and the regeneration of 11-*cis*-retinal increases.

Photoreceptor cells produce ATP from glucose mainly via oxidative phosphorylation and to a lesser extent via glycolysis [8], and thus large

mitochondria are found densely packed in the photoreceptor inner segments. Glucose and oxygen are supplied from the capillary network of the choroid that lies close to the photoreceptors (Figs. 1a and 2a). The oxygen consumption of the retina is appr. 20 % higher than the oxygen consumption reported for the brain [5].

The Role of the Retinal Pigment Epithelium

Together with the retina, the RPE is among the most metabolically active tissues in the body. The RPE serves many functions. First, melanin in RPE cells absorbs light that has passed through the retina in order to prevent light scattering and to reduce light-induced damage. Second, the tight junctions between RPE cells form a barrier between the choroid and photoreceptors [9]. Analogous to the blood-brain barrier, this blood-retinal barrier controls exchange between blood and retina and thus maintains the specialized environment of the photoreceptors. The barrier function of the RPE is physically supported by Bruch's membrane that acts as a semipermeable molecular sieve [2]. At the same time, RPE cells utilize glucose transporters that allow passive transport of glucose from the choroid to the photoreceptors [10]. Third, the RPE is involved in the regeneration of 11-*cis*-retinal. All-*trans*-retinal (see above) detaches from the opsin and is enzymatically reduced to all-*trans*-retinol. Retinoid binding proteins shuttle the retinol from the outer segments to the RPE, where the rest of the retinal metabolism takes place. Here, all-*trans*-retinol is first esterized with palmitate, then isomerized to 11-*cis*-retinol, and finally, oxidized to 11-*cis*-retinal. The latter is transported back to the outer segment, where it spontaneously reacts with opsin to regenerate rhodopsin, thus completing the visual cycle.

Finally, the RPE is of utmost importance for the regeneration of the photoreceptor outer segments. The strong illumination of the outer segments in a high-oxygen environment can lead to photochemical damage. If the energy from a photon is transferred from a light-absorbing molecule to oxygen, reactive oxygen species (e.g., singlet oxygen) can be created. Those can break molecular bonds or induce photooxidation. Accumulation of such events can ultimately lead to damage of the outer segments. Therefore, photoreceptor outer segments must be constantly renewed. Around sunrise, the tips of the outer segments are shed off and are phagocytosed by RPE cells, while new discs are added at the bases of the outer segments [11]. Complete renewal of the rod outer segment takes approximately 10 days. Due to the high amount of material, phagocytosis in RPE cells is metabolically demanding. Some of the breakdown products may be recycled, while others are discharged into the choriocapillaries. Some undigested proteins, lipids, and retinoids remain as an aggregation complex called lipofuscin [9]. Chemical reactions between these components lead to the formation of retinoid-lipid complexes in lipofuscin, the so-called bisretinoids [12]. Lipofuscin can absorb light, shows autofluorescence, and is susceptible to photochemical changes. Lipofuscin accumulation is thought to contribute to the development of age-related macular degeneration (see chapter "Age-related macular degeneration").

Inside-Out: Signals from the Eye Affecting Other Organs and Tissues

The impact of the eye on other organs results mainly from the projection of the retinal output neurons, the ganglion cells, which relay the signals from the retina via their axons to the brain. Most of the ganglion cell output provides the basis for visual information processing that involves at least 30 % of the cerebral cortex.

Recently, a class of ganglion cells has been described that serves an entirely different function. These ganglion cells express their own photopigment called melanopsin, which is distantly related to rhodopsin. This cell class provides input to the suprachiasmatic nucleus (SCN) in the brain (together forming the retinohypothalamic tract). The SCN functions as pacemaker, responsible for the generation of the circadian clock. Retinal input from the melanopsin-containing ganglion cells

resets the clock in the SCN every day [13]. SCN cells project to the paraventricular nucleus of the hypothalamus – a site of hormone production. The projection from the SCN to the pineal gland controls the release of melatonin, the "hormone of the night" that is involved in the regulation of our sleep-wake cycle. Circadian rhythms also influence body temperature, blood pressure, and heart frequency (see chapters "Migraine and cluster headache" and "Rheumatoid arthritis").

Outside-In: Signals and Metabolites Affecting the Function of the Eye

Vitamin A, the precursor of retinal, is an essential vitamin [14]. It is stored in the liver (see chapter "Overview" under part "Liver") and transported in the blood (see chapter "Overview" under part "Blood") by retinoid binding proteins. RPE cells absorb vitamin A from the choroidal circulation and convert it to retinal to supply the photoreceptors. As retinal is pivotal for rhodopsin function, lack of vitamin A may lead to night blindness.

Diabetes (see chapter "Diabetes mellitus") can affect the performance of the eye in two major ways. First, in the lens, glucose can be converted into sorbitol, which is later – but more slowly – converted into fructose [15]. Under normal conditions, only small amounts of sorbitol are synthesized. However, unphysiologically high blood glucose levels cause excess sorbitol production, which results in osmotic swelling of the lens (as sorbitol and fructose cannot leave the lens and thus are highly osmotic) that can ultimately lead to lens clouding, i.e., cataract. Second, diabetes triggers pathological changes in retinal blood vessels. In early diabetic retinopathy (the so-called non-proliferative stage), retinal blood vessels become blocked, which results in reduced nourishment and oxygen supply. In response to the hypoxic state, in a second phase (called proliferative diabetic retinopathy), new blood vessels are formed. These vessels are thinner, mechanically less stable and their endothelial cells form a less effective blood-retinal barrier. Consequences are bleedings into the retina and vitreous as well as scar formation and detachment of the retina. Diabetic retinopathy may ultimately lead to blindness.

Final Remarks

The main functions of the eye are to provide visual information about our environment and to synchronize our internal clock to the day/night cycle. Partial or total blindness can be induced by several mechanisms, including the destruction of retinal ganglion cells and optic nerve due to an increase in intraocular pressure, as in glaucoma (see chapter "Glaucoma"), or the loss of photoreceptor cells triggered by photochemical damage or other factors, such as in age-related macular degeneration (see chapter "Age-related macular degeneration").

References

1. Masland R (2012) The neuronal organization of the retina. Neuron 76:266–280
2. Booij JC, Baas DC, Beisekeeva J, Gorgels TG, Bergen AA (2010) The dynamic nature of Bruch's membrane. Prog Retin Eye Res 29:1–18
3. Hunter JJ, Morgan JI, Merigan WH, Sliney DH, Sparrow JR, Williams DR (2012) The susceptibility of the retina to photochemical damage from visible light. Prog Retin Eye Res 31:28–42
4. Shui YB, Fu JJ, Garcia C, Dattilo LK, Rajagopal R, McMillan S, Mak G, Holekamp NM, Lewis A, Beebe DC (2006) Oxygen distribution in the rabbit eye and oxygen consumption by the lens. Invest Ophthalmol Vis Sci 47:1571–1580
5. Yau KW, Hardie R (2009) Phototransduction motifs and variations. Cell 139:246–264
6. Okawa H, Sampath AP, Laughlin SB, Fain GL (2008) ATP consumption by mammalian rod photoreceptors in darkness and in light. Curr Biol 18: 1917–1921
7. Ames A 3rd, Li YY, Heher EC, Kimble CR (1992) Energy metabolism of rabbit retina as related to function: high cost of Na^+ transport. J Neurosci 12: 840–853
8. Wong-Riley M (2010) Energy metabolism of the visual system. Eye Brain 2:99–116
9. Cunha-Vaz JG (1976) The blood-retinal barriers. Doc Ophthalmol 41:287–327

10. Senanayake P, Calabro A, Hu JG, Bonilha VL, Darr A, Bok D, Hollyfield JG (2006) Glucose utilization by the retinal pigment epithelium: evidence for rapid uptake and storage in glycogen, followed by glycogen utilization. Exp Eye Res 83:235–246
11. Kevany BM, Palczewski K (2010) Phagocytosis of retinal rod and cone retinal. Physiology (Bethesda) 25:8–15
12. Keller JN, Dimayuga E, Chen Q, Thorpe J, Gee J, Ding Q (2004) Autophagy, proteasomes, lipofuscin, and oxidative stress in the aging brain. Int J Biochem Cell Biol 36:2376–2391
13. Berson D (2003) Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci 26:314–320
14. D'Ambrosio DN, Clugston RD, Blaner WS (2011) Vitamin A metabolism: an update. Nutrients 3: 63–103
15. Kinoshita JH (1965) Pathways of glucose metabolism in the lens. Invest Ophthalmol 4:619–628