

## 2.1 Introduction

The retina remains the best studied part of the human brain. Embryologically part of the central nervous system [1–5], but readily accessible to examination, it can be investigated with relative ease by both scientists and clinicians. Moreover, an estimated 80% of all sensory information in humans is thought to be of retinal origin [6], indicating the importance of retinal function for the ability to interact with the outside world. In this chapter, we examine the retina's unique cytoarchitecture and how it is assembled to give rise to its sophisticated neurocircuitry. Most of our knowledge is based on studies in primates and adult humans, but reference is made to the development of the retina wherever possible.

## 2.2 Anatomy of the Retina

### 2.2.1 Topographic Organization of the Retina

The adult *posterior pole* (anatomic macula or area centralis) is about 4.5–6 mm in diameter, centered on the fovea, and located between the superior and inferior temporal arcades. The *macula* (anatomic fovea centralis) is located approximately 3 mm temporal to the

optic disc and is about 1.5 mm, or one disc size, in diameter [7]. The center of the macula lies just below the horizontal meridian [8], a relationship that is used to study rotation during incyclo and excyclotorsion. The presence of xanthophyll, a yellow carotenoid pigment, gives the region its name – the macula lutea.

The most central part of the macula, the *fovea* (anatomic foveola), is formed by a central, circa 0.35 mm-wide depression and represents the retinal region of greatest visual acuity [9]. Clinically, it is recognized by the foveal reflex, blunting or loss of which may indicate early macular disease. The foveola is demarcated by a sloping wall, the clivus, which contributes to the annular light reflex that is seen in children and young adults. The foveola has the highest density of cone photoreceptors (199,000/mm<sup>2</sup>), which are narrowed and elongated in this location to maximize light detection further [10]. The long axons of the foveal cones form Henle's layer as they radiate out of the central depression. The fovea develops by an opposing process of outward displacement of the cells of the inner nuclear and ganglion cell layers, while the cone photoreceptors migrate toward the center [11–13]. Rod photoreceptors are excluded from the foveal outer retina ("rod-free zone"). As a result, the foveola contains only cone photoreceptors and some Müller cells. The central 500 µm of the fovea contains no retinal capillaries (the *foveal avascular zone* [FAZ]), making the fovea dependent on blood supply from the choriocapillaris. The exact extent of the FAZ can be delineated with accuracy only by fluorescein angiography. Retinal blood vessels from the temporal retina do not cross the central fovea but arc around it.

The *peripheral retina* comprises the remaining retina outside the temporal retinal arteries. Anatomically, the peripheral retina possesses only one layer of ganglion cells. The ampullae of the vortex veins lie just posterior

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to the equator, while the long posterior ciliary arteries and nerves mark the horizontal meridian. The *ora serrata* delineates the anterior termination of the sensory retina and the beginning of the pars plana of the ciliary body. At this junction, the sensory retina is reduced to a single cell layer which, anteriorly, becomes the nonpigmented ciliary epithelium whereas the retinal pigment epithelium (RPE) is replaced by pigmented ciliary epithelium. Junctional complexes between the pigmented and nonpigmented ciliary epithelia abolish the potential subretinal space that exists between the RPE and the neuroretina, making the pars plana a relatively safe site for surgical access to the posterior segment.

### 2.2.2 Cellular Organization of the Retina

The major cellular components of the retina are the RPE cell, the photoreceptor cells, the interneurons, the ganglion cells, and the glial cells. Vascular cells are described in greater detail later.

#### 2.2.2.1 Retinal Pigment Epithelium

Like the sensory components of the neuroretina, the RPE cell is of neuroectodermal embryonic origin [1–5, 14, 15]. Each adult human retina contains about 3.5 million RPE cells [16] whose diameters vary four-fold between 14  $\mu\text{m}$  in the central retina and 60  $\mu\text{m}$  in the peripheral retina [17]. The density of RPE cells is greater in the fovea (5,000 cells/ $\text{mm}^2$ ) than in the periphery (2,000 cells/ $\text{mm}^2$ ) [18]. In the central retina, where RPE cells are most tightly packed, they take the shape of regular hexagonal tiles that form a single layer of cuboidal epithelium. Tight junctions between adjacent RPE cells form the outer blood-retina barrier, an important physiologic barrier to the free flow of molecules between the leaky choriocapillaris and the photoreceptors of the neuroretina [19–25].

Cellular polarity and the abundance of mitochondria, endoplasmic reticulum, and free ribosomes all indicate a very high level of metabolic activity in the RPE cell [23, 24, 26]. Infoldings of the basal and apical surfaces greatly increase the RPE surface area, facilitating active transport across its cell surface with both the choriocapillaris and the photoreceptor layer [7, 18, 24, 27–29]. Though normally nondividing cells,

the RPE can proliferate in response to a variety of pathological conditions. Melanin renders the RPE dark brown to black. It is synthesized from tyrosine via the tyrosinase pathway [30]. Pigmentation of the RPE is a rapid process that begins at about 35 days gestation and is complete within approximately 1 week [31]. Pigmentation of choroidal melanocytes, in contrast, does not start before the fifth month of fetal life and continues postnatally. Unlike choroidal melanocytes, which are neural crest-derived, RPE cells show no or little racial variation in melanin pigmentation. Another pigment, lipofuscin, accumulates as an end-product of outer photoreceptor segment degradation in the RPE and in Bruch's membrane. Though lipofuscin is a pigment of aging, small amounts of it can already be detected in the RPE of children [28].

#### 2.2.2.2 Photoreceptors

The photoreceptors are the sensors of the visual system that convert the capture of photons into a nerve signal in a process called phototransduction [32]. The human retina contains approximately four to five million cones and 77–107 million rods [32–34]. Only cones are found in the foveola, whereas rods predominate outside the foveola in the remaining fovea and all of the peripheral retina. Among the three cone photoreceptors, red cones (63% or 2.9 million) are more common than green (32% or 1.4 million) and blue cones (5% or 0.2 million) [9]. Each photoreceptor consists of an outer segment (photopigment), inner segment (mitochondria, endoplasmic reticulum), a nucleus, an inner fiber (analogous to an axon), and the synaptic terminal [35]. The outer segment contains the photon-capturing photopigment. Opsin is a transmembranous protein that anchors the photopigment in the plasma membrane. In the outer segments, the plasma membrane is stacked into hundreds of flat discs, thereby increasing the density of retinal-opsin photopigment per photoreceptor cell. The discs in cones are deep invaginations of the outer segment membrane, while in rods, the discs are separate from the outer segment (except at the base). Shed discs are phagocytosed by the RPE. A nonmotile cilium connects the outer and inner segments. The inner segment contains the cellular machinery necessary to meet the high metabolic requirements of the photoreceptor cells. Its outer portion (the ellipsoid) is packed with mitochondria that produce ATP by oxidative

phosphorylation, while the inner portion (the myoid) contains smooth and rough endoplasmic reticulum for synthetic activity as well as microtubules for intracellular transport. The photoreceptor nucleus contains all nonmitochondrial DNA. The inner fiber is the axon of the photoreceptor cell and transmits the photoreceptor cell signals to the outer plexiform layer (OPL) via its synaptic terminals. Due to the absence of inner nuclear layer cells in the foveola, foveolar inner fibers have to travel to the OPL in the surrounding macula to make synaptic contact. The synaptic neurotransmitter of the photoreceptor cell is glutamate, which is released in response to depolarization. The photoreceptor is most depolarized in darkness, whereas phototransduction results in graded hyperpolarization. The terminal endings of the photoreceptors interact with neighboring photoreceptors and interneurons (horizontal and bipolar cells) and play a critical physiological role in the transmission and early processing of visual information in the retina.

### 2.2.2.3 Interneuron Cells

Interneurons in the inner nuclear retinal layer connect the photoreceptor layer with the ganglion cell layer. These interneurons consist of the bipolar, horizontal, amacrine, and interplexiform cells, which form complex neuroretinal circuitries in the outer and inner plexiform layers (IPLs) that process the photoreceptor signal and transmit this information to the ganglion cell layer. In the simplest case, the photoreceptor cell is directly connected to a ganglion cell via a bipolar cell. *Bipolar cells* receive input from either rods or cones [6, 36, 37]. Cone bipolar cells may make contact with as few as one cone, while rod bipolar cells may receive input from up to 70 rods. Depending on their response to glutamate, bipolar cells are classified as being hyperpolarizing (OFF-center) or depolarizing (ON-center). Photoreceptors also interact with *horizontal cells* in the OPL [38]. Three types of horizontal cells have been described in the human retina [39, 40]. *Amacrine cells* are mainly found in the inner nuclear layer, although some are seen in the ganglion cell layer and the IPL as well [41]. There are as many as 30 different types of amacrine cells, though the functional significance of each of these is not fully understood [34]. Amacrine cells are classified according to the size of their horizontal dendritic fields and the sublamina level(s)

within the IPL in which they synapse. The dendritic fields of amacrine cells vary between less than 100  $\mu\text{m}$  (narrow-field) and greater than 500  $\mu\text{m}$  (large-field) [39]. Similarly, amacrine cells are uni-, bi-, or multi-stratified, creating connections both within and between the different strata of the IPL. Examples of different amacrine cell types are the narrow-field, multistratified AII amacrine cell that is involved in scotopic vision, and the wide-field starburst amacrine cell that is involved in motion detection [34]. Another interneuron in the inner nuclear layer – the *interplexiform cell* – has processes extending into the inner and outer plexiform layers. Thus, on their way to the ganglion cell, visual signals are transmitted and modified by bipolar, horizontal, amacrine, and interplexiform cells as part of the visual processing within the retina [38].

### 2.2.2.4 Ganglion Cells

Finally, the ganglion cells are responsible for transmitting visual information from the retina to the brain. The ganglion perikarya are located in the ganglion cell layer, while their dendrites make contact with bipolar and amacrine cells in the IPL. Up to 20 different ganglion cell types have been described in the human retina – the two best known types are the midget and the parasol cells, which make up about 80% of ganglion cell population [34]. The *midget ganglion cell* (also known as P or  $\beta$  cell) receives input from midget bipolar cells at a ratio of up to one-to-one in the fovea. It is a small cell with a relatively small dendritic arbor. The *parasol ganglion cell* (M or  $\alpha$  cell) has a much more extensive dendritic arbor that resembles an opened umbrella in histological preparations of the retina. Midget and parasol cells project to the parvocellular and magnocellular layers of the lateral geniculate nucleus (LGN), respectively [42, 43]. Because of the anatomic distance between the retina and the brain, the ganglion axons require effective mechanisms for transport of metabolites and organelles away from (anterograde) and back to (retrograde) the ganglion cell nucleus. Axonal transport occurs at slow (<10 mm/day), high (hundreds of mm/day), or intermediate velocities. Most transport is slow and anterograde. An example of fast anterograde transport involves the transfer of vesicles containing neurotransmitter to the axonal synapses. Axon transport is an active process that requires adenosine triphosphate (ATP), which is

supplied by the mitochondria in the axon. Interference with anterograde transport at the lamina cribrosa results in pathologic disc swelling.

### 2.2.2.5 Glial Cells

Four glial cell types are found in the retina: Müller cells, astrocytes, microglia, and occasionally, oligodendrocytes. *Müller cells* are the main glial cells of the retina [29, 44–46]. Their perikarya are located in the inner nuclear layer with cell processes that span the entire neuroretina [29]. The proximal extensions of Müller cells expand and flatten to form so-called *endfeet* whose basal lamina forms the *inner limiting membrane* [47]. Distally, Müller's extensions give rise to the *outer limiting membrane* by forming a series of junctional complexes. Lateral extensions of Müller cells surround the retinal neurons. Müller cell processes also cover retinal blood vessels. Müller cells play a crucial role in maintaining the local environment that allows the visual process to function optimally. *Astrocytes* are thought to derive from stem cells in the optic nerve and are found in the superficial layers of the neuroretina where they surround ganglion cells, nerve fibers, and superficial retinal blood vessels [48]. *Microglia* enter the retina from the circulation [48]. They are phagocytic and part of the reticuloendothelial system. They are usually found in small numbers in the nerve fiber layer, but are mobile and can reach any part of the retina. *Oligodendrocytes* give rise to the myelin sheath in the peripheral nervous system. Though normally unmyelinated, retinal nerve fibers occasionally are seen to be myelinated, indicating that oligodendrocytes can reach the retina in certain conditions.

## 2.2.3 General Histological Organization of the Retina

The retina is the neurosensory component of the eye. Its outer part is supplied by a vascular layer, the choroid, and protected by a tough outer layer, the sclera. The cellular elements of the retina are arranged and adapted to meet the functional requirements of the different regions of the retina. As we will see, the regional differentiation of the retina is a process of slow maturation that takes several years to be completed.

### 2.2.3.1 Bruch's Membrane

This membrane separates the choriocapillaris from the RPE. It is an elastic membrane composed of five layers: the basement membrane of the choriocapillaris, an outer collagenous layer, a central elastic layer, an inner collagenous layer, and the basement membrane of the RPE. It stretches from the optic disc at the posterior pole to the ora serrata anteriorly and varies in thickness between 2 and 4  $\mu\text{m}$  at the posterior pole and 1–2  $\mu\text{m}$  at the ora serrata. With age, Bruch's membrane grows thicker and its ultrastructure becomes less distinct. The composition of Bruch's membrane is complex and consists of elastin, different types of collagens (types I–V, IX, XI, XII), as well as several adhesive glycoproteins, including fibronectin and laminin, which help to anchor cells to Bruch's membrane.

### 2.2.3.2 Retinal Pigment Epithelium

Each eye contains about 3.5 million RPE cells [16], which are held together by junctional complexes to form a continuous epithelial monolayer. The tight junctions (zonulae occludentes) between these RPE cells separate the choriocapillaris from the photoreceptors of the outer retina, thus creating the outer blood-retina barrier, a selective barrier between the outer retina and its choroidal blood supply [19–25]. This barrier helps to control the extracellular milieu and maintain the function of the outer retina. During embryogenesis, the central neuroectoderm of the optic vesicle invaginates to form the inner leaf of the optic cup and becomes the sensory retina. The peripheral neuroectoderm of the optic vesicle forms the pigmented outer leaf of the optic cup and differentiates into the retinal pigment epithelium. As a result of this invagination, the neuroretina and the retinal pigment epithelium become apposed, being only separated by a potential subretinal space, which can fill with fluid and give rise to a retinal detachment.

### 2.2.3.3 Photoreceptor Layer

Rods and cones are tightly stacked together into a single pallisading layer of photoreceptors [32, 33, 35, 49–51]. This thin, subcellular stratum is the only light-sensitive part of the neuroretina and the site of

phototransduction. All other layers of the neuroretina collectively serve to process and transmit these nerve signals.

#### 2.2.3.4 External Limiting Membrane

This is not a true membrane, but created by junctional complexes between adjacent Müller cells as well as between Müller and photoreceptor cells. The subretinal space is a potential space lying between the outer blood retina barrier and the external limiting membrane [52, 53].

#### 2.2.3.5 Outer Nuclear Layer

The outer nuclear layer contains the nuclei of the photoreceptor cells and is thickest in the foveolar area. The human retina contains approximately four to five million cones and 77–107 million rods [32–34]. Only cones are found in the foveola, whereas rods predominate outside the foveola throughout the remaining retina. The maximum rod density is found in the “rod ring” about 4.5 mm, or 20–25°, from the foveola [6]. The absence of rods from the foveola (“rod-free zone”) accounts for the physiological central scotoma that is experienced under extreme scotopic conditions.

#### 2.2.3.6 Outer Plexiform Layer

In the OPL, photoreceptor cells of the outer nuclear layer form connections with the bipolar and horizontal cells of the inner nuclear layers. This is an important initial processing step in the retina: Individual cone photoreceptor signals are connected in such a way that they give rise to concentric receptive fields with an antagonistic center-surround organization. These signals are then transmitted to the next layer of processing, the IPL, by bipolar cells [30, 54]. The OPL has two components: the axons of the photoreceptor, bipolar and horizontal cells and their synaptic connections. The axons of the photoreceptor cells transmit the photosignal to the OPL and form a specialized structure, Henle’s fiber layer, in the central retina. The terminals of the photoreceptor cells – the rod spherules and cone pedicles – form the synapses between the photoreceptor, bipolar and horizontal cells [34, 38].

#### 2.2.3.7 Inner Nuclear Layer

This layer harbors the nuclei of not less than five different types of cells: the horizontal, the bipolar, the amacrine, the interplexiform, and the Müller cells. The horizontal cells are located along the outer limit of the inner nuclear layer facing the OPL, whereas the amacrine faces the IPL. The nuclei of the bipolar, interplexiform, and Müller cells take up intermediate positions [29, 34, 38].

#### 2.2.3.8 Inner Plexiform Layer

The IPL is the second retinal processing layer with networks between bipolar, amacrine, and ganglion cells. The IPL shows sublayering into six lamina. This enables the parallel representation and processing of the photoreceptor input through specific interactions between the bipolar, amacrine, and ganglion cells in each of the six lamina of the IPL [54].

#### 2.2.3.9 Ganglion Cell Layer

This layer contains about 1.2 million ganglion cells as well as a number of other cell types, including “displaced” amacrine cells, astrocytes, endothelial cells, and pericytes [32, 48, 55]. The thickness of the ganglion cell layer is greatest in the perifoveal macula consisting of between eight and ten rows of nuclei (60–80 µm), decreases to a single row outside the macula (10–20 µm), and is absent from the foveola itself [6, 7]. The small midget and the larger parasol cells make up 80% of the ganglion cell layer and behave as either ON or OFF cells depending on the location of their dendrites in the ON or OFF-regions of the IPL. The ON-OFF center-surround organization of receptive fields that was first created in the OPL is thus maintained at the ganglion cell level [33, 34, 54].

#### 2.2.3.10 Nerve Fiber Layer

Ganglionic axons travel towards the optic nerve head within the nerve fiber layer. Thin and difficult to discern in the far periphery, the nerve fiber layer becomes thicker towards the disc as a result of the convergence of all retinal ganglion axon fibers on the optic disc.



The axons are accompanied by astrocytes in the nerve fiber layer and are separated into small bundles by the cellular processes of Müller cells and the internal limiting membrane [36, 56]. The exact cross-sectional ordering of the axonal fibers of the peripheral and central ganglion cells in the retina remains controversial [37–40].

Temporal to the disc lies the macula, which has the highest density of ganglion cells. Axons from the macula project straight to the disc, forming the papillomacular “bundle.” The remaining axons of the temporal retina reach the optic disc only by arcing around the papillomacular bundle. As a result, all temporal ganglion cell axons originating from outside the macula are compressed into the superotemporal and inferotemporal sectors of the optic nerve, above and below the temporal entry of the papillomacular bundle fibers. The superior and inferior nerve fibers are therefore much thicker (almost 200  $\mu\text{m}$ ) compared to the papillomacular bundle (65  $\mu\text{m}$ ) and easier to see on clinical examination, especially in red-free light. Nasally, axons enter the nasal half of the optic disc more or less straight. In addition, ganglion axon fibers do not cross the horizontal meridian (the horizontal raphe).

#### 2.2.3.11 Inner Limiting Membrane and Vitreoretinal Interface

The innermost processes of the Müller cell enlarge and flatten on the vitreal side to form the inner limiting membrane. Vitreous collagen fibrils insert into this membrane of the retina, so rendering the retina vulnerable to vitreoretinal traction forces [47].

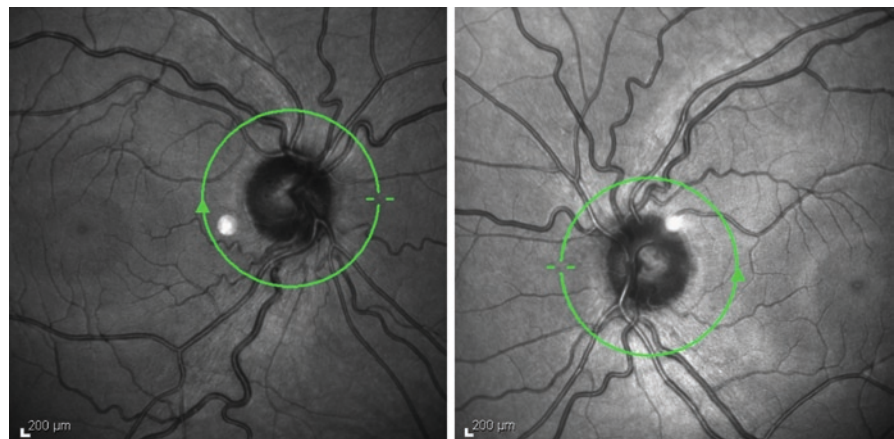
### 2.2.4 Special Histological Organization of the Fovea

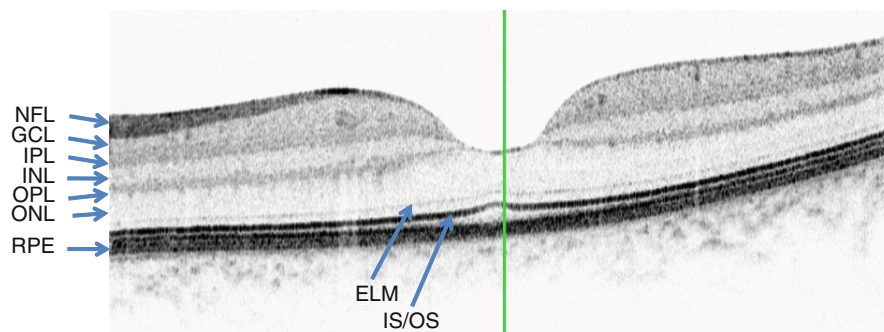
Though the posterior pole (the anatomic macula) makes up less than 4% of the entire retina, it accounts for all central and most photopic vision [41]. Because of its special histological organization, the posterior pole is subdivided into four concentric regions: the perifovea, the parafovea, the foveal slope, and the foveola [41].

The *perifovea* is the outermost region of the anatomic macula that borders the peripheral retina. It is rich in retinal blood vessels and has a high rod–cone ratio of 33–130:1, an increased cone density compared with the peripheral retina, and a ganglion cell layer that is greater than a single cell layer in thickness. The *parafovea* is located between the fovea and the perifovea. It contains less retinal vessels, has a reduced rod: cone ratio of 4:1, and has the highest density of ganglion cells. The fovea contains the *foveola*, a flat central depression in the fovea and the site of maximum visual acuity. The foveola is surrounded by the *foveal slope* or clivus. Importantly, the clivus marks the switch from vascular to avascular retina (the FAZ) and from rod-dominated to cone-dominated retina [41] (Figs. 2.1 and 2.2).

The foveola itself is created in two opposing tissue migrations: the slow peripheral displacement of the inner nuclear and ganglion cells, while red and green cone photoreceptors in the surrounding outer retina migrate towards the foveola [11–13]. As a result of these migrations, the fovea thins and forms a central depression, the foveola. The foveola is populated by cone photoreceptors and Müller cells only. Rods are excluded from the foveolar depression, so are blue cones, all ganglion and inner retinal cells, blood

**Fig. 2.1** Red-free fundus views (Spectralis™, Heidelberg Engineering, Germany) of both eyes of a healthy 9-year-old boy showing the normal striations, especially of the superior and inferior nerve fiber layer (NFL). Note also the normal tiny foveolar reflex in each eye and the physiological degree of excyclotorsion of each macula relative to the optic disc. The annular reflex can also be seen in the left eye





**Fig. 2.2** Enhanced fine structural detail in vivo of the layered macular cytoarchitecture as seen on spectral (Fourier) domain ultra-high resolution OCT (7  $\mu\text{m}$  axial resolution (in tissue), 14  $\mu\text{m}$  transverse resolution (in tissue); Spectralis™, Heidelberg Engineering, Germany). *NFL* nerve fiber layer (left papillomac-

ular bundle); *GCL* ganglion cell layer; *IPL* inner plexiform layer; *INL* inner nuclear layer; *OPL* outer plexiform layer; *ONL* outer nuclear layer; *ELM* external limiting membrane; *IS/OS* inner/outer segment junction; *RPE* retinal pigment epithelium

vessels, and other glial cells [41, 57]. The human rod-free zone constricts from 2.00 mm<sup>2</sup> at 22 fetal weeks to less than 0.40 mm<sup>2</sup> at 45 months [11]. As a result of this concentration, the highest density of cone photoreceptors in the adult human retina is produced, varying between 100,000 and 324,000 cones/mm<sup>2</sup> [33]. In the adult, the rod-free zone is 350  $\mu\text{m}$  in diameter, or 1° of visual angle [33]. In this most tightly packed foveolar region, the foveolar cones are compressed to about 1–1.5  $\mu\text{m}$  and elongated to 70  $\mu\text{m}$  [43]. The inner fibers of the foveolar cone remain in contact with the bipolar and horizontal cells during their peripheral displacement and become considerably elongated. The radial arrangement of these axonal fibers in the clivus gives rise to Henle's layer. While the absence of retinal vessels in the FAZ removes a source of optical impediment, it also means that the central fovea is entirely dependent on blood supply from the choriocapillaris. Ganglion axons from the temporal retina do not cross the fovea, but arc around the fovea.

The density of cones falls rapidly from an average peak of 199,000 cells/mm<sup>2</sup> in the foveola to about 20,000/mm<sup>2</sup> at the edge of the fovea and about 5,000/mm<sup>2</sup> outside the fovea. The functional consequence of this extreme specialization of foveal organization is that, though maximal central visual acuity can be generated in a very small area of the entire retina under photopic conditions, visual acuity is already halved at 1° eccentricity, quartered at 5° eccentricity, and is brought to less than 10% outside the temporal arcades, while the rod-free foveola is functionally blind under extreme scotopic conditions [9].

## 2.2.5 Blood Supply of the Retina

Apart from the foveolar avascular zone (FAZ) and the extreme retinal periphery, which are thin enough to be supplied by diffusion from the choroidal circulation, the remaining human retina is too thick to be supplied by either the retinal or the choroidal circulation alone. The reason for this dual dependence is that diffusion time increases by the square of the distance. It has been calculated that it takes a glucose molecule 50 ms to diffuse 10  $\mu\text{m}$ , but 100 times longer (5 s) to reach 100  $\mu\text{m}$  [44]. The choroidal circulation thus supplies the outer retina, whereas the inner retina is supplied by the retinal circulation [45, 46, 48]. The oxygen tension is lowest in the watershed area between the two circulations [47].

### 2.2.5.1 Choroidal Circulation

The choroid receives 80% of all ocular blood compared with 15% to the iris/ciliary body and 5% to the retina [58]. The outer retina, containing the RPE and the photoreceptors, is avascular and depends on the vascular support provided by the adjacent choroid. In the presence of cilioretinal vessels, the choroid can also supply the inner retina. The choroidal circulation is fed by the ophthalmic artery via the medial and lateral posterior ciliary arteries, each of which gives rise to one long and several short posterior ciliary arteries. Apart from minor contributions from recurrent branches of the long posterior ciliary arteries, essentially all blood in the choriocapillaris is supplied by the short posterior

arteries, which enter the posterior globe close to the optic nerve [44]. The short posterior ciliary arteries also contribute to the vascular circle of Haller and Zinn that supplies the optic nerve head. The choroid varies in thickness between 0.25 mm posteriorly and 0.1 mm anteriorly and consists of three different vascular layers: [1] the outermost layer of Haller with large valveless veins that drain into the three to six vortex veins; [2] the intermediate layer of Sattler; and [3] the choriocapillaris [50, 51, 57, 59]. The choriocapillaris is a single layer of densely arranged capillaries separated from the RPE by Bruch's membrane. The anatomic distance between the choriocapillaris and the photoreceptors is less than 20  $\mu\text{m}$  facilitating rapid diffusion [44]. Experiments in monkeys have shown that the choroid has by far the highest blood flow per unit time and weight of any other ocular or nonocular tissue examined [47, 52, 53], and this high flow is maximal at the fovea and close to the optic disc [53]. Though the choriocapillaris supplies both the RPE and the photoreceptor layers, the choriocapillaris also requires a healthy RPE for its own formation and maintenance [18, 46].

#### 2.2.5.2 Hyaloid Circulation

Though transient, the hyaloid vasculature is important for two reasons: Firstly, it provides the early intraocular circulation, especially to the rapidly growing avascular lens, before gradually involuting during the second and third trimesters. Secondly, the posterior (nonvitreal) segment of the hyaloid artery becomes the central retinal artery and gives rise to the retinal circulation by lateral sprouting.

The hyaloid circulation is composed of, from posterior to anterior, the hyaloid artery, the vasa hyaloidea propria, the tunica vasculosa lentis, and the pupillary membrane. The hyaloid artery is a branch of the primitive dorsal ophthalmic artery and enters the optic cup from the optic stalk via the optic fissure, assuming a central position in the later optic nerve [5]. The hyaloid artery grows towards the lens and expands into the dense capillary system of the tunica vasculosa lentis and the pupillary membrane. In addition, the tunica vasculosa lentis forms radial anastomoses with the annular vessel, which are fed by the choroidal circulation of the optic cup. It is thought that hyaloid vascular development is partly driven by vascular endothelial growth factor (VEGF), which is expressed by the lens [46].

The hyaloid vasculature is the main component of the primary vitreous and is gradually replaced by the secondary (mature vitreous) and the tertiary vitreous (lens zonules and vitreous base) [4, 5]. The hyaloid circulation is programmed to involute between 12 and 36 weeks gestation in the following order: the vasa hyaloidea propria, followed by the tunica vasculosa lentis, the pupillary membrane, and, finally, the hyaloid artery itself [3]. Recent studies have shown that the mechanisms of involution involve both apoptosis and necrosis [54]. Juxtavascular hyalocytes in the surrounding secondary vitreous may partly mediate the involution of the hyaloid vessels of the primary vitreous [54]. Usually, the only vestige of the highly vascularized primary hyaloid circulation is the canal of Cloquet. However, incomplete involution of the hyaloid circulation is seen in up to 3% of full-term babies [60]. Other remnants include persistent pupillary membrane fibers, a Mittendorf dot, vitreous cysts, a persistent hyaloid artery, a Bergmeister's papilla, and persistent primary hyperplastic vitreous (PHPV) or persistent fetal vasculature (PFV) [5, 61–64].

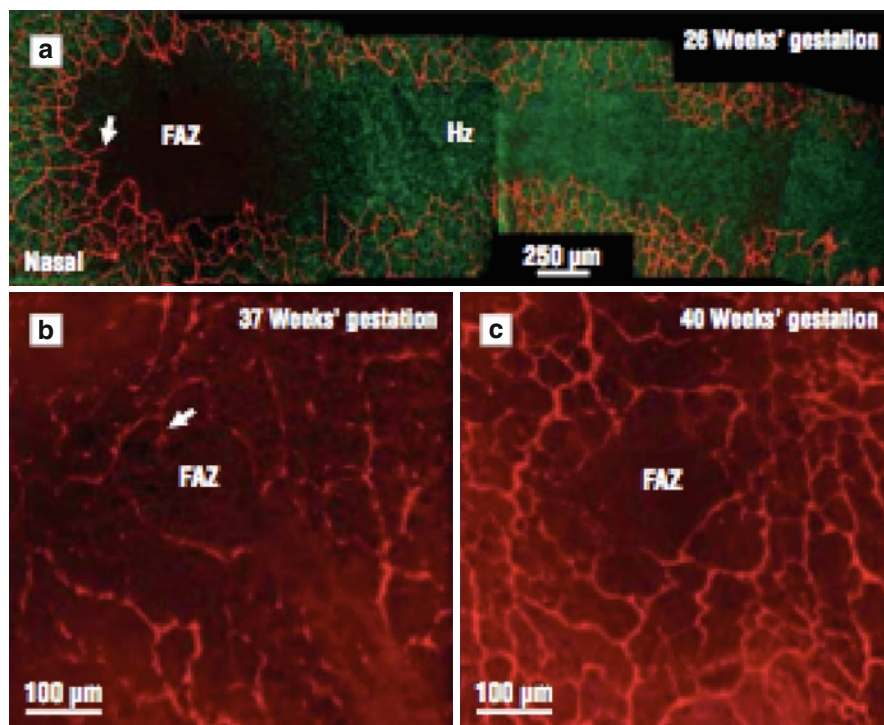
#### 2.2.5.3 Retinal Circulation

Retinal vascularisation commences from the optic disc around 14–15 weeks gestation and proceeds centrifugally towards the retinal periphery [46, 48, 65]. This process is not completed till the last month of gestation. The classic concept of retinal vascularization was said to occur in two steps: First, the generation of new endothelial tissue from vascular precursor cells by *vasculogenesis*, followed subsequently by the proliferation of existing endothelial cells by *angiogenesis*. However, this concept has been questioned by those who have argued that all retinal vascularization is angiogenic [46, 48, 66–70]. An important molecular mediator of this process again is VEGF, which acts as an endothelial mitogen and survival factor [46]. Its spatial and temporal expression by retinal astrocytes and Müller cells is tightly controlled and is critical in the formation, remodeling, and maintenance of the retinal circulation in health and disease [46, 65, 67, 71–73].

The central retinal artery branches off the ophthalmic artery almost immediately after entering the orbit and enters the optic nerve about 1 cm behind the globe [58]. It pierces the dura mater and the arachnoid before entering the optic nerve itself [74]. The central retinal



**Fig. 2.3** Retinal whole mounts at 26, 37 and 40 weeks' gestation. Rods (*green*) are absent from the foveal region. CD31/factor VIII reactive retinal blood vessels (*red*) delineate the foveal avascular zone. Reproduced, with permission from Provis and Hendrickson [80]



artery subsequently emerges from within the optic cup to give rise to the retinal circulation with its four main branches, the superior and inferior temporal and nasal retinal arteries. The retinal arteries are endarterial and travel outwards towards the peripheral retina within the nerve fiber layer. The smaller arterioles give rise to two types of capillary systems: horizontal branches supply the superficial nerve fiber layer, whilst deep branches enter the retina to form between one (periphery and perifoveal) and four (peripapillary) horizontal capillary layers in the inner retina, depending on retinal thickness [75]. The retinal circulation thus supplies all layers of the neuroretina except the photoreceptor layer, which is avascular and dependent on the chorio-capillaris. All retinal capillary blood is returned via retinal venules into the central retinal vein, which, after exiting the optic nerve, drains either into the ophthalmic veins or into the cavernous sinus directly [44], though other drainage systems, such as into the pterygoid plexus, may also occasionally exist.

The anatomical arrangements of the retinal circulation have important clinical implications [7, 76–79]. Though the retinal blood supply is dual, it is nonoverlapping, making the retina doubly vulnerable to the loss of either the retinal or the choroidal circulations.

Secondly, the retinal circulation has an endarterial arrangement, i.e., the interruption of a retinal arteriole results in the loss of arterial supply to that part of the capillary bed. Thirdly, the arterial and venous vessels affect each other due to their physical proximity. For instance, arterial hypertension may cause a retinal artery to compress the adjacent retinal vein at a crossing point. Finally, the low hydrostatic pressure in the venous system makes the retinal veins particularly susceptible to external compression caused by raised intraocular, intraorbital, or intracranial pressure. The temporal retinal vessels curve around the fovea and an important feature, the FAZ has been commented on above. It is interesting to note that recent evidence discounts the theory that the fovea is initially vascularised and that these vessels subsequently regress. Provis and Hendrickson [80] have recently shown that the fovea is avascular throughout development (Fig. 2.3).

#### 2.2.5.4 The Outer and Inner Blood-Retina Barriers

Similar to the blood-brain barrier [80], the retina is protected by a blood-retina barrier system with an inner

component [20–22] and an outer component [19, 20, 22, 25], which together control the retinal microenvironment. The inner blood-retina barrier surrounds all retinal blood vessels and is formed by tight junctions that seal the intercellular spaces between the nonfenestrated retinal endothelial cells [81]. The outer blood-retina barrier is formed by tight junctions between the retinal epithelial cells. Very small molecules, such as  $O_2$  and  $CO_2$ , and lipophilic molecules can diffuse across the barriers.

### 2.2.5.5 Regulation of Blood Flow to the Retina

Maintenance of the retinal milieu is also achieved by the tight control of retinal blood flow and rate [81, 82]. The flow rate through a capillary bed is controlled by regulation at the level of the precapillary arteriole, which is modified by both central and local factors [45, 82, 83]. Central mechanisms regulate the overall distribution of blood in the organism and involve both direct autonomic innervation as well as the indirect effects of adrenal and other humoral factors (e.g., angiotensin, vasopressin) [44]. Local factors affect autoregulation in response to the conditions in local tissues. Local autoregulation occurs not only in response to changes in hydrostatic pressure (the myogenic reflex) but also in response to metabolic fluctuations in  $O_2$ ,  $CO_2$ , pH, temperature, and adenosine [44, 82]. The choroidal circulation has strong central sympathetic controls with little or no autoregulation. By contrast, the retinal circulation lacks sympathetic innervation and is controlled by autoregulation instead [81, 82, 84].

Blood is delivered to the retinal tissues by a vascular system that is geometrically designed in accord with the principles of maintaining both steady state and minimum work – Murray's law [85]. According to this principle, the total flow of any vascular system is carried by a set of vessels whose radii cubed sum a constant value [86]. The fractal geometric dimensions that are seen in normal retinæ are disturbed in disease [87]. Retinal vessel bifurcation angles may reflect microvascular density and, if this is low, a narrower angle results, as has been reported in men who were born with low birth weights. Accordingly, the temporal retinal vessel angle falls between relatively narrow limits and exhibits a considerable degree of interocular symmetry [88].

## 2.2.6 Optic Nerve

The retinal ganglion axon fibers travel within the nerve fiber layer to converge on the optic disc while obeying strict retinotopic organization. The adult optic nerve head is typically elliptical in shape, having a slightly greater mean vertical (1.9 mm) than mean horizontal (1.7–1.8 mm) diameter [32], though its size and shape can vary greatly even in healthy eyes [32, 55, 89–91]. In children, the optic disc and optic nerve achieve 75% of their adult size around term and 95% before the end of the first postnatal year [92]. The retinal axons leave the retinal plane to enter the optic nerve head at an angle of about  $90^\circ$  taking up position in a specific order: central RCG axons are located in the inner part of the optic nerve rim whilst peripheral RCG axons are found in the outer layers of the optic disc rim. The central part of the optic nerve head that contains no retinal fibers and appears optically empty forms the optic cup. The relationship between disc and cup size (the cup-disc ratio) can vary widely in healthy eyes [91].

All retinal ganglion axons pass through the optic nerve head, which consists of three parts: the preliminary portion (between the lamina cribrosa and the vitreous), the lamina cribrosa, and the postlaminar portion. Surrounded by astrocytes in the prelaminar portion, the axon bundles stream through the foramina of the lamina cribrosa, which is made of condensations of scleral collagen, to enter the postlaminar portion where oligodendrocytes and connective tissue become part of the glial structure. A number of histological structures delineate the prelaminar optic nerve head from the vitreous (*internal limiting membrane of Elschnig* with the *central meniscus of Kuhnt*), the retina (*intermediary tissue of Kuhnt*), and the choroid (*border tissue of Jacoby*). In the oligodendrocyte-containing postlaminar portion, the axon fibers become myelinated and the optic nerve ensheathed by the meninges.

After passing through the optic nerve disc, the retinal axons travel in the intraorbital (about 30 mm), the intracanalicular (5–12 mm), and the intracranial portions of the optic nerve (8–19 mm). At the optic chiasma, the nasal fibers decussate to join the temporal fibers of the contralateral optic nerve to form the optic tract, which projects to the LGN, the pretectal nuclei, the superior colliculus, the hypothalamus, and possibly other brain structures [32].

The blood circulation of the optic nerve head is primarily by the *circle of Zinn and Haller* and the

peripapillary choroid of the posterior ciliary artery circulation [32, 55, 76]. The central retinal artery circulation makes significant contributions only to the superficial optic nerve fiber layer (not the prelaminar portion of the optic nerve head) and the posterior portion of the optic nerve head. Thus, the posterior ciliary artery circulation supplies both the outer retina via the choriocapillaris and most of the optic nerve head. However, unlike the fenestrated capillaries of the choriocapillaris, the capillaries of the optic nerve head are nonfenestrated with tight junctions. In addition, the optic nerve head vessels are capable of autoregulation unlike the choriocapillaris. Even though the optic nerve head circulation is derived from the posterior ciliary circulation, its blood-retina barrier function and capability to autoregulate resemble more the retinal than the choroidal circulation [55].

Because all retinal ganglion cell axons and all retinal blood vessels have to pass through the optic disc, relatively small lesions at the optic disc and in the optic nerve can have devastating clinical effects [79, 93]. Pathology affecting these ganglionic axons along their anatomic course between the retina and the brain gives rise to characteristic visual field defects [94, 95] and patterns of neural rim loss and pallor [90, 96–99] that help to localize lesions clinically.

### 2.2.6.1 Physiology and Development

Unlike the graded responses seen in photoreceptors, retinal ganglion cells generate all-or-nothing action potentials, which are transmitted to the brain. Myelination of the retinal ganglion axon has important physiological effects in this regard: Myelination minimizes the need for ion channels by restricting these to the *nodes of Ranvier*, thus achieving saltatory conduction from one *node of Ranvier* to the next. Because conduction does not require the depolarization of the entire course of the axon, saltatory conduction is both faster and less energy-consuming [32]. In humans, myelination starts in the brain and gradually extends towards the eye. Myelination of the optic tract and the intracranial optic nerve is slow and not complete until term, while the intraorbital optic nerve is not myelinated until about 7 months after birth, though the process may take even longer than 2 years [32, 100]. The mechanisms underlying myelination are not fully understood. It is thought that the

optic nerve head acts as a barrier to oligodendrocytes and their precursors, the O-2A cells, effectively preventing them from migrating into the retina [32].

Much progress has been made in understanding the cellular and molecular mechanisms for normal and abnormal axon growth [101–105]. It is clear that an excess number of retinal ganglion cells is produced early during prenatal development. Up to 70% of axons in the human fetal optic nerve die between 16 weeks (3.7 million) and 29 weeks of gestation (1.1 million) [106]. The excess production is thought to be required to achieve the subsequent selection of axons that make correct contact with their brain targets. After this rapid elimination of more than two million ganglion cells early in human fetal development, axonal cell decline is gradual by an estimated 5,000 axons per year of life [32].

## 2.3 Physiology of the Retina

### 2.3.1 The Retinal Pigment Epithelium

The RPE is among the most metabolically active tissues in the body. It is not directly involved in vision, however. Its role is essentially supportive, and loss of the RPE results in secondary atrophy of adjacent photoreceptors and the choriocapillaris. A healthy RPE is therefore vital for the survival and function of the photoreceptors and choriocapillaris and is essential for achieving and maintaining full visual function [24]. To this end, the main functions of the RPE consist in disposing of the photoreceptor outer segments, participating in retinoid metabolism and the visual cycle as well as in controlling the chemical milieu of the subretinal space [18, 23, 24].

#### 2.3.1.1 Role in the Turnover of the Photoreceptor Outer Segments

Light irradiation in a high-oxygen environment results in the production of free radicals and damage to lipid membranes in the photoreceptor outer segments. Being nondividing permanent cells, the photoreceptors are particularly vulnerable to the accumulation of peroxidation damage, a problem which they have solved by regularly shedding their outer segments. Outer

segment shedding exhibits diurnal variation and is faster for rods than for cones. In the monkey, the time required to replace the entire rod outer segment is 9 days in the peripheral retina and 13 days in the parafoveal retina.

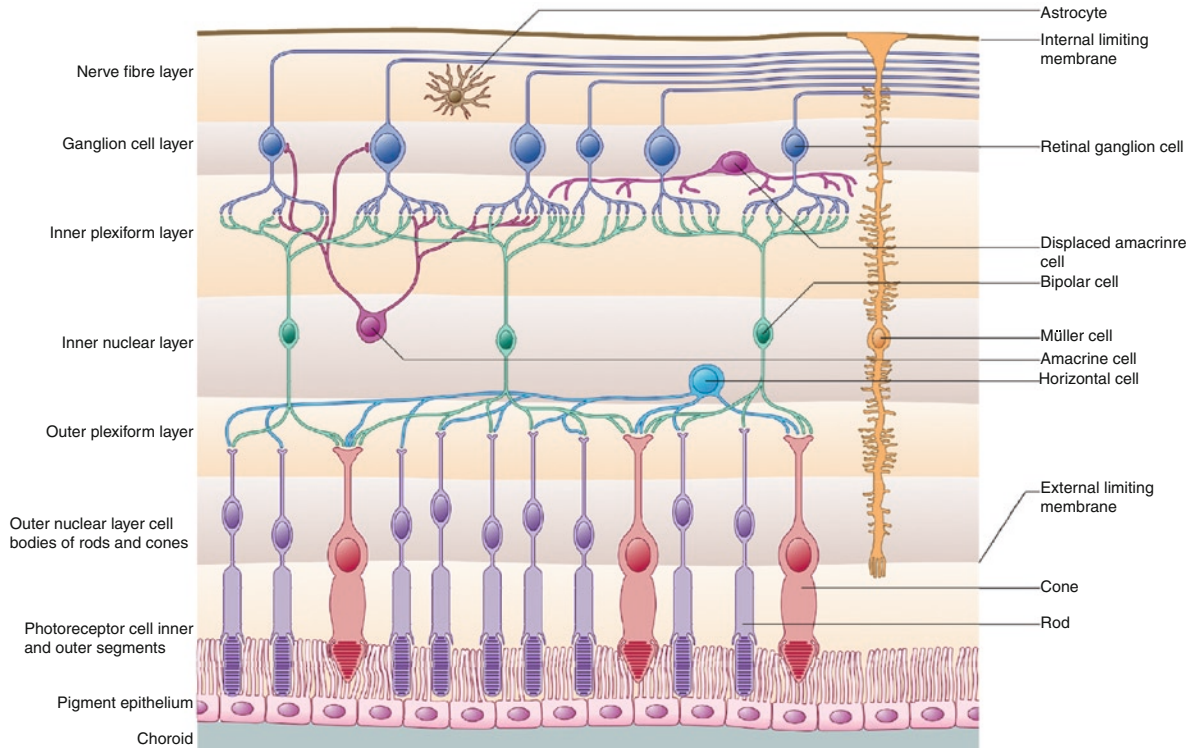
Each RPE cell is in contact with an average of 45 photoreceptors in the human retina [17]. RPE microvilli phagocytose the distal tips of the outer segments. Undigested material is egested and cleared from Bruch's membrane via the choriocapillaris. Large amounts of outer segment lipid membranes are thus disposed of by the RPE cell – upwards of 4,000 discs per day.

### 2.3.1.2 Participation in Retinoid Metabolism and the Visual Cycle

Moreover, the RPE is crucial in providing and recycling vitamin A, as well as other retinoids involved in the visual cycle, thus ensuring the constant regeneration of the chromophores in the photoreceptors [18, 23, 24, 107].

Retinol is an essential vitamin that humans cannot synthesize *de novo*. Retinol therefore has to be supplied

in the diet. It is stored in the liver and transported in the blood by a carrier protein called serum retinol-binding protein (RBP). The RPE cell absorbs retinol from the choroidal circulation across the basal surface and supplies the photoreceptors via its apical surface. The light-sensitive chromophore in the photoreceptor is 11-*cis*-retinaldehyde, which is bound to a large trans-membranous protein, opsin, that anchors the photopigment into the outer segment membrane. During phototransduction, 11-*cis*-retinaldehyde is converted to all-*trans*-retinol. All-*trans*-retinol is transported back to the RPE where it is isomerized to 11-*cis*-retinol and then reoxidized to 11-*cis*-retinaldehyde to complete its regeneration. 11-*cis*-retinaldehyde is returned to the photoreceptor cell where it recombines with opsin, completing the visual cycle. The retinol and retinal molecules are chaperoned by special binding proteins: In the subretinal space, interphotoreceptor retinoid-binding protein (IRBP) shuttles retinol from the photoreceptor to the RPE and retinal back to the photoreceptor, whilst cellular retinol-binding protein (CRBP) and cellular retinaldehyde-binding protein (CRALBP) protect retinol and retinal inside the cell [18, 23, 24] (Fig. 2.4).



**Fig. 2.4** Overview of retinal neurocircuitry – from Gray's anatomy



### 2.3.1.3 Transport and Barrier Function of the RPE

The RPE forms the outer blood retinal barrier. This barrier effect is achieved by tight intercellular junctional complexes, which stop the free passage of ions and larger molecules between the choriocapillaris and the RPE [23, 24]. At the same time, the RPE has active and facilitated transport mechanisms for ions and molecules, which maintain the finely balanced extracellular environment of the outer retina [23, 24, 29]. In addition, the RPE provides the pump function that keeps the subretinal space dehydrated, thus maintaining the normal apposition of the neuroretina with the RPE [52, 53]. This pump function is essential, as there are no firm attachments per se between the RPE and the neuroretinal outer segments and as the interphotoreceptor matrix (IPM) only forms a weak viscous bond. The retinal adhesive force across the subretinal space is energy-dependent and diminishes within minutes of ischemia [52].

The RPE has a number of further functions: It secretes a large number of local growth factors and cytokines, including VEGF, ciliary neurotrophic factor, fibroblast, and platelet-derived growth factors [24], and contains superoxide dismutase, catalase, glutathione, melanin, ascorbate, and other antioxidants that protect the RPE against the effects of oxidative damage [17]. In addition to its antioxidant effects, melanin also absorbs scattering light and blocks external light from reaching the retina through the sclera directly. The RPE is also likely to contribute to the maintenance of the eye as an immune-privileged site through the secretion of immunomodulatory cytokines [23].

### 2.3.2 Visual Physiology and the Sensory Retina

The cytoarchitecture and neurocircuitry of the retina provide the anatomic basis that initiates the visual process under conditions of both low and high illumination. In this process, the retina and subsequently the brain construct an increasingly sophisticated visual representation of the external world [9, 54, 75, 108–110]. The term vision encapsulates a range of different physiological functions, some of which are

conscious whilst others are not. The retina contains two functionally and structurally different light-detection systems: The first, and best known, is image-forming and provides detailed information about the environment with high spatial and temporal resolution, culminating in our ability to make out shapes, depth, color, and motion [110–119]. This requires specialized photoreceptors in the outer retina and the processing by interneurons in the outer and inner retina [30, 34, 38, 43]. By contrast, nonimage-forming vision is concerned with ambient luminance and involved in the pupil response to light, the setting of the circadian cycle (circadian photoentrainment) and probably other functions as well [120–125]. Recently, a subset of ganglion cells was discovered, which are intrinsically photosensitive (pRGCs), i.e., they can capture light in the inner retina themselves and transmit this information directly to the brain in the absence of rods and cones [126]. These pRGCs contain a new photopigment, melanopsin, which renders these retinal ganglion cells photosensitive *sui generis* [124, 127–132].

### 2.3.3 Image-Forming Visual System

#### 2.3.3.1 Detection of Photons by Visual Pigment in the Photoreceptor Cell

The photoreceptor cells are the sensors of the image-forming visual system. They enable the neuroretina to detect photons and to generate a physiological nerve signal through a process called phototransduction [35, 133–137]. To achieve this, photoreceptors contain visual pigments that consist of two components: a small, light-sensitive molecule, or chromophore, called 11-*cis* retinal (an aldehyde of vitamin A), and a larger protein, called opsin. The chromophore is covalently bonded to the opsin protein to form a retinal-opsin complex. Whilst the retinal molecule is common to all photopigments, molecular differences in opsin give rise to differences in absorption peaks and spectra. Human retinæ contain four retinal-opsin complexes: one rod photopigment (rhodopsin) and three cone photopigments. The three cone pigments are classified based on their respective maximum absorption in humans at 419 nm (“blue,” S or short wavelength-sensitive), 531 nm (“green,” M

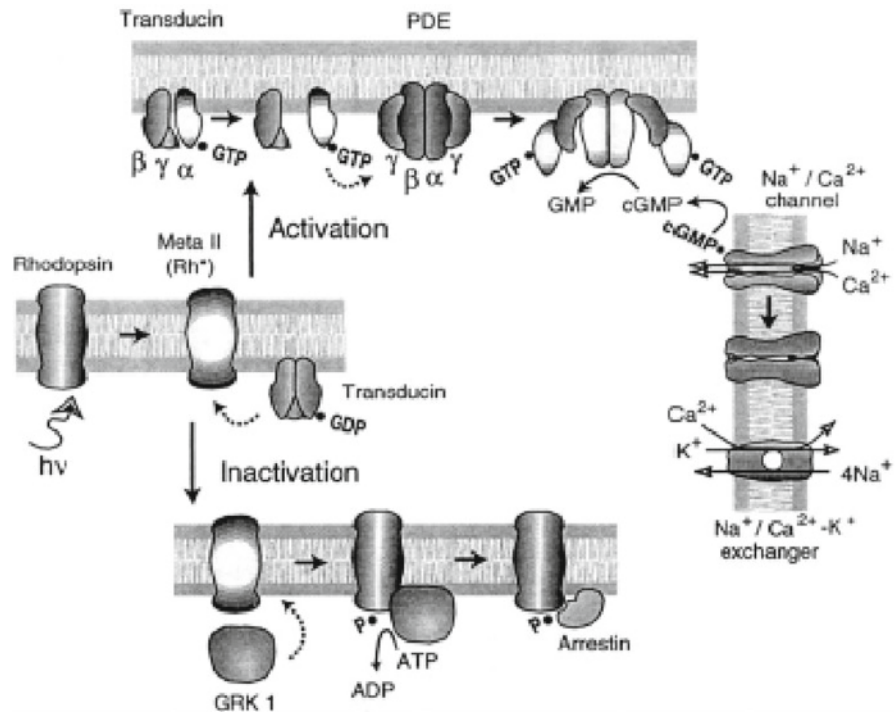


or medium wavelength-sensitive) and 558 nm (“red,” L or long wavelength-sensitive), while the peak absorption of rhodopsin is 496 nm (blue–green) [108]. Photoreceptors are therefore classified as cones, which are either maximally green, red, or blue sensitive, or as rods. In human retinal development, L/M opsins are expressed later than S opsins [138, 139]. Moreover, L/M opsin expression spreads in an expanding wave-front to the peripheral retina, which is initially expressing S opsin only. In human retinæ, 5–10% of cones in this advancing L/M opsin wave-front express both S and L/M opsins during the fetal and neonatal period before diminishing to 0.01–0.03% in the adult retina, suggesting that some cones may initially express S opsin before switching to L/M opsins [140] (Fig. 2.5).

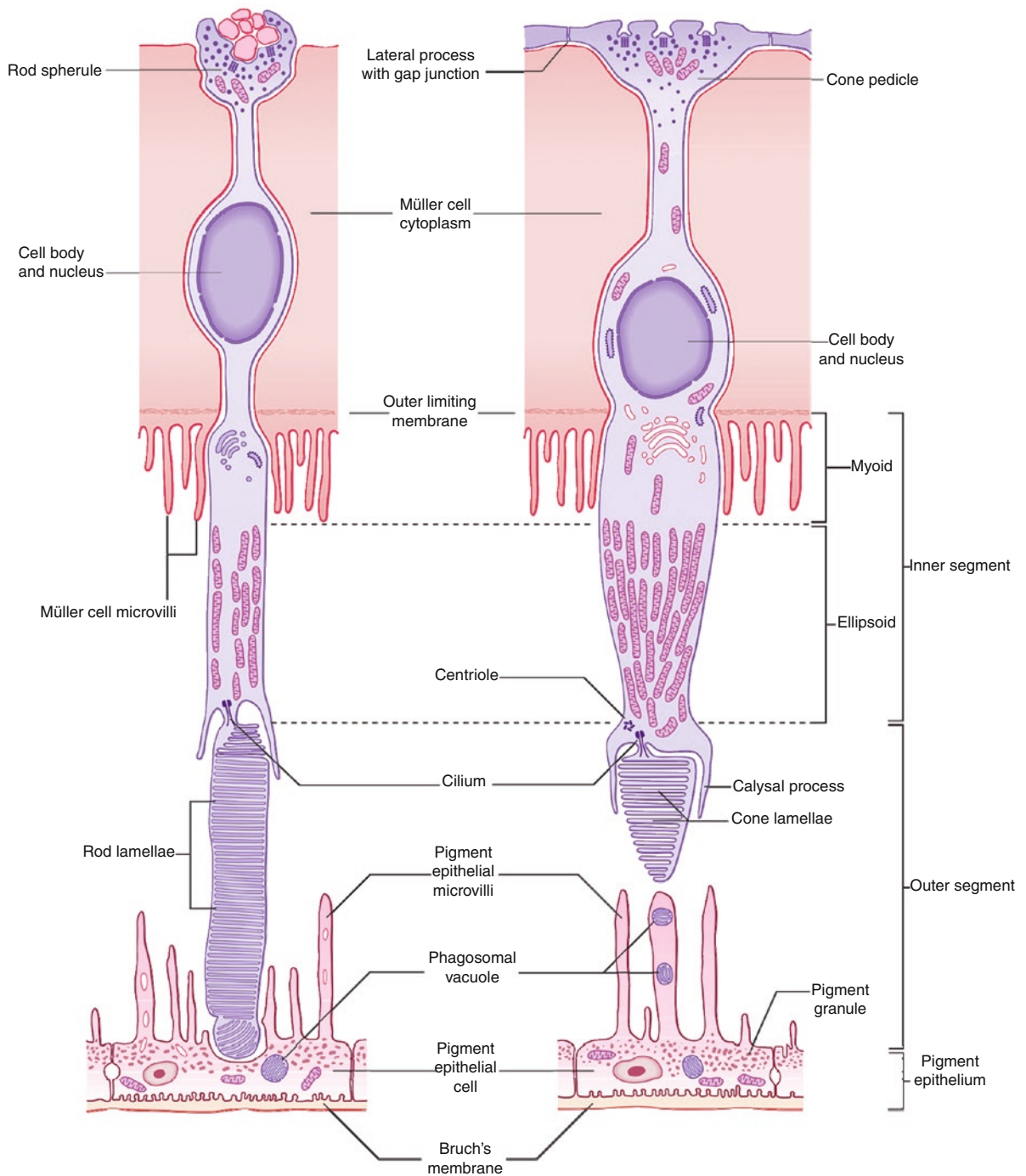
Rods are exquisitely light sensitive and function best under scotopic conditions. Fully dark adapted rods are capable of detecting a single light photon. By comparison, cones are relatively light insensitive, and many more photons are needed to cause a similar electrical signal from a cone. Rods are achromatic and give rise to low resolution, thus vision is grey and relatively poor in dim light. With increasing

illumination, cones are activated, adding color and greater temporal and spatial resolution. Because of the dual population of the retina of rod and cone photoreceptors, visual function is endowed with greater scope and complexity, being possible both in daylight and at night, albeit with different qualities and sensitivities (“duplex retina”).

Opsin precursor is synthesized by the rough endoplasmic reticulum in the inner segment, converted to opsin in the Golgi apparatus and incorporated into the photoreceptor membrane by vesicular transport [32]. Once embedded in the photoreceptor membrane, opsins migrate from the inner segment past the connecting cilium into the outer segment to cover the membrane of the outer segment discs. The ability of photoreceptor cells to detect photons depends, in part, on how many photopigments can be packed into the outer segment. Rod and cone outer segments are densely packed with discs, thus vastly increasing the disc surface area available for photopigments. It has been estimated that a rod photoreceptor with 1,000 discs may contain 150,000,000 rhodopsin molecules. In bright sunlight, this rod cell may be exposed to 1,000,000 photons per second [108] (Fig. 2.6).



**Fig. 2.5** Schematic diagram illustrating mechanisms of activation and inactivation in vertebrate photoreceptors (Reprinted with permission from Fain et al. (2001) Adaptation in vertebrate photoreceptors. Phys. Reviews. 81: 117–150. Copyright 1999 by The President and the Fellows of Harvard College. Reprinted by permission of Harvard University Press)



**Fig. 2.6** Photo receptor architecture – from Gray's anatomy

### 2.3.3.2 Light Activation of the Photopigment

In phototransduction, a cascade of intracellular events convert the absorption of single photons into a physiologic response of the entire photoreceptor cell that signals the detection of light to other cells in the retina. This process is increasingly understood at the molecular level and has shed light on the molecular pathogenesis of a number of retinal conditions [141–143]. Basically, the activation of an intracellular second-messenger system links the molecular events on the surface of the disc membrane, where photons are captured, with the activity of cation channels on the outer segment cell membrane, where the membrane potential is controlled. The messenger that carries this signal across the cytosol is cGMP (3'-5'-cyclic guanosine monophosphate), a small molecule that controls the function of cation channel in the cell membrane of the outer segment.

The initial event in phototransduction is the activation of the photopigment. During light absorption, energy is transferred from the photon to the photopigment, causing the break of one of the double bonds in the retinal molecule. This transient break permits the isomerization of 11-*cis* retinal to all-*trans* retinal. The transition of 11-*cis* retinal to all-*trans* retinal is the only step that is light dependent during vision. This conformational change of the retinal molecule also causes a conformational change in the structure of the surrounding opsin molecule, resulting in the activation of the photopigment. The light-activated opsin binds to transducin, a G protein that is found on the cytosolic surface of the disc membrane, and activates it. Transducin activates cGMP phosphodiesterase (PDE), an enzyme that reduces the concentration of cyclic GMP by catalyzing its conversion into 5'-GMP (5'-guanosine monophosphate). cGMP is the second messenger, and reduced intracellular concentrations of cGMP cause the closure of the cGMP-gated cation channels in the outer segment cell membrane, resulting in the hyperpolarization of the photoreceptor.

The photoreceptor membrane potential is generated by ion channels and ion pumps along the inner and outer segment [108]. Special cGMP-gated cation channels in the outer segment create an inward current of  $\text{Na}^+$  (and  $\text{Ca}^{++}$ ) into the cell. This influx of  $\text{Na}^+$  (and  $\text{Ca}^{++}$ ) is regulated by the presence (gate open) or absence (gate closed) of cGMP. Flow of positively

charged  $\text{Na}^+$  into the cell depolarizes the cell. At the same time,  $\text{K}^+$  – selective channels in the inner segment facilitate the outward current of  $\text{K}^+$ . Flow of  $\text{K}^+$  out of the cell hyperpolarizes the photoreceptor.  $\text{K}^+$  is pumped back into the photoreceptor and  $\text{Na}^+$  transported out of the cell by active  $\text{Na}^+$  - $\text{K}^+$  pumps in the inner segment. A  $\text{Na}^+$  - $\text{K}^+$  and  $\text{Ca}^{++}$  exchanger in the outer segment facilitates  $\text{Na}^+$  influx into the cell in exchange for  $\text{K}^+$  and  $\text{Ca}^{++}$  efflux out of the cell. Crucially, the second messenger cGMP regulates only the cGMP-gated cation channels in the outer segment, but not the  $\text{K}^+$ -selective pores, the active  $\text{Na}^+$  - $\text{K}^+$  pump or the  $\text{Na}^+$  - $\text{K}^+$  and  $\text{Ca}^{++}$  exchanger. Because in darkness the intracellular cGMP concentration is highest, most cGMP-gated cation channels are open resulting in the inward flow of  $\text{Na}^+$  and the depolarization of the photoreceptor (so-called dark current). In light, the activation of cGMP PDE causes the reduction of intracellular cGMP and the closure of the cGMP-gated cation channels, leading to the hyperpolarization of the photoreceptor. The degree of hyperpolarization is dependent on the amount of photon absorption per unit time. Photoreceptors therefore respond to light stimulation by gradation, not by an all-or-nothing action potential, and by hyperpolarization rather than depolarization. Depolarization of the photoreceptor membrane releases glutamate (the neurotransmitter at the photoreceptor terminal), while light-induced hyperpolarization of the photoreceptor inhibits the release of glutamate.

The generation of a cellular signal following the absorption of photons is made possible by the powerful biochemical amplification built into the phototransduction cascade. In fact, it is thought that a single activated rhodopsin molecule may activate about 800 G protein molecules during an estimated activated life-time of 50 ms, each of which, in turn, is thought to activate one PDE and to cause the degradation of six cGMP molecules. In other words, the activation of a single rhodopsin has resulted in the removal of an estimated 4,800 cGMP molecules, or 2% of all free cGMP, causing a detectable 2 mV hyperpolarization of the photoreceptor cell [108]. At the same time, it is vital that this powerful amplification mechanism can rapidly be switched off to get the photoreceptor ready for the next phototransduction event. This is achieved by the rapid inactivation of the activated photopigment by enzymatic phosphorylation and

binding to arrestin, the inactivation of transducin and PDE, and the rapid resynthesis of cGMP by guanylate cyclase [134, 137, 144].

### 2.3.3.3 Retinal Integration in the Plexiform Layers

The photoreceptor feeds into the neurocircuitry of the OPL of the retina. Visual information is processed by both horizontal and vertical pathways within the retina and is ultimately transmitted to the ganglion cell layer of the inner retina. The regions of retinal integration are principally the outer and IPLs.

In the OPL, the photoreceptor cells interact with horizontal and bipolar cells. The *horizontal cells* (HI-III) mediate the horizontal integration of the photoreceptors in the OPL and contribute towards the generation of contrast enhancement [30, 34, 38]. In addition to feeding into these horizontal pathways, photoreceptors also interact with *bipolar cells* directly. Bipolar cells connect the outer with the inner retina by transmitting the processed photoreceptor and horizontal cell signals to the IPL.

In fact, bipolar cells provide not just one, but multiple, parallel, vertical pathways. A number of different bipolar cells have been described: Rod bipolar and blue cone bipolar cells are innervated by rods and blue cones, while red and green cones connect to at least eight different bipolar cells: two midget bipolar cells (one ON/OFF each) and six diffuse bipolar cells (3 ON and 3 OFF each). Midget bipolar cells have small dendritic and axonal arbors. In the central retina, they have a 1:1 ratio with cones and ganglion cells. Diffuse bipolar cells have larger arbors and receive input from multiple cones. Like the ganglion cells, the receptive fields of bipolar cells are antagonistic with a center-surround organization, i.e., visual stimulation of the center and the periphery of the same receptive field have opposing effects.

Simultaneous innervation of the cone photoreceptors by ON and OFF bipolar cells splits the cone signal into parallel ON- and OFF- pathways, which consist of cones, ON/OFF cone bipolar, and ON/OFF ganglion cells. Whether bipolar cells are ON- or OFF-cells depends on their response to the release of glutamate. *OFF bipolar* cells are inactivated by light (they hyperpolarize) while ON cells are activated (they depolarize).

This happens because OFF bipolar cells have sign-conserving synapses, i.e., OFF bipolar cells are hyperpolarized by the hyperpolarization of the photoreceptor cell and depolarized by the depolarization of the photoreceptor. Conversely, *ON bipolar* cells have sign-inverting synapses, i.e., ON bipolar cells respond to the hyperpolarization of photoreceptors in light with depolarization (activation) and to photoreceptor depolarization in darkness with hyperpolarization (inactivation). These different physiological responses of ON and OFF bipolar cells to the release of glutamate by the cones are due to the action of their different glutamate receptors: In OFF bipolar cells, the glutamate receptor is coupled to a cation channel (ionotropic), which opens in the presence of glutamate, causing bipolar depolarization. In ON bipolar cells, the glutamate receptor acts via a G protein, resulting in the closure of ion channels and the hyperpolarization of the bipolar cell [54].

In the IPL, the cone bipolar cells can interact with amacrine and ganglion cells in six different sublamina. Thus, parallel transmission and processing of signals from the same photoreceptors generate multiple, functionally different retinal maps in the different sublamina of the IPL, all in response to the same light stimulation reflecting the processing power of the retina.

Many morphologically different *amacrine cell* types participate in retinal processing. Horizontally, their dendritic fields range from less than 100  $\mu\text{m}$  to greater than 500  $\mu\text{m}$ . Moreover, these amacrine cells are uni-, bi-, or multistriate, thus creating interactions both within as well as between the six different strata of the IPL. In addition to their morphological diversity, amacrine cells also use an unusual number of different neurotransmitters, including GABA, glycine, acetylcholine, dopamine, and peptide neurotransmitters. The precise functions of each of these amacrine cell types are not understood yet. The most common amacrine cell, the AII cell, plays a crucial role in the rod pathway by linking the rod bipolar cell with the ON- and OFF- cone bipolar pathways, while starburst amacrine cells are thought to play a role in directional selectivity/optokinetic eye movements and probably retinal development [34, 38].

All visual information converges on the *ganglion cell* [145]. Like the amacrine cell, ganglion cells differ in their dendritic field size and the level(s) of the IPL in which they synapse with bipolar and amacrine cells

[38, 54]. Though the two most common types of ganglion cells are the midget and the parasol ganglion cells, many more types of ganglion cells have been described. Midget ganglion cells are more numerous and smaller than the parasol cells and have a small dendritic arbor with synapses in the IPL. Centrally, the midget ganglion cell makes contact with only one midget bipolar cell. The parasol ganglion cells also ramify in the IPL, although their dendritic arbors are considerably larger. Most ganglion cells have a concentric receptive field with an antagonistic center-surround organization and form parallel ON- and OFF-pathways. The functional benefit of the antagonistic center-surround arrangement is the generation of enhanced contrast.

The vertical pathways for scotopic and photopic vision differ. The *cone pathway* involves only three neurons: the cone, bipolar, and ganglion cells, and segregates into ON- and OFF pathways in the OPL [34, 146]. In the *rod pathway*, the rod relays to the rod-bipolar cell type, but instead of synapsing with ganglion cells directly, the rod-bipolar cell innervates the AII amacrine cell in the inner nuclear layer. It is the AII amacrine cell that then makes contact with the ON/OFF-cone bipolar cells, thereby joining the classical rod and cone pathways [36]. Thus, the classical rod pathway is split only after joining the ON- and OFF-cone pathways in the IPL. Because of the large convergence of many rods on a single amacrine AII cell, it has been suggested that the classical rod pathway is best at operating in scotopic light conditions. However, further rod pathways are thought to exist that are likely to mediate rod function under mesopic or low photopic conditions. They probably involve direct rod-cone coupling or even rod photoreceptor/cone bipolar contacts [34, 36, 37].

### 2.3.4 Nonimage-Forming Visual System

It has long been recognized that there are a number of visual functions that are concerned with the detection of ambient light levels rather than the visual image itself. These include the pupillary response to light and the entrainment of the circadian pacemaker [120–125]. In mammals, bilateral enucleations abolish circadian photoentrainment demonstrating that circadian

synchronization is dependent on ocular photoreception in mammals [123, 125, 147–149].

It was long assumed that ocular photoreception was mediated exclusively by rod and cone photoreceptors. However, recent studies have shown that nonrod, non-cone type ocular photoreceptors must exist in the mammalian retina that are involved in nonimage-forming vision [123, 125, 128, 148, 150–152]. Such a non-rod, noncone ocular photoreceptor was described in the inner retina by Berson and coworkers in 2002 [126] when they identified a distinct subset of retinal ganglion cells, which responded directly to light even when these cells were pharmacologically and physically dissociated from the rest of the retina. Because these ganglion cells were intrinsically photosensitive, they were termed pRGCs (photosensitive retinal ganglion cells) [123, 126]. Additional evidence of the existence of short-wavelength photosensitive RGCs has recently been published from studies in humans without rods or cones [153, 154].

Photosensitive retinal ganglion cells have different properties compared with the rod and cone photoreceptors in the outer retina. The pRGC exhibits distinctive maxima of sensitivity to light stimulation at around 484 and 482 nm in rodents and primates, respectively [126, 155]. In response to light, the pRGCs depolarize unlike rods and cones, which hyperpolarize and produce action potentials rather than the graded responses of rods and cones [126]. Moreover, the pRGCs are not as light-sensitive and react more slowly to light than rod and cone photoreceptors [120, 124]. The pRGC makes dendritic contacts in the IPL only and, unlike the rods and cones, projects directly to the brain [126, 153, 155].

The putative photopigment of the pRGC is melanopsin [120, 121, 124, 127, 128, 132]. Deletion of the melanopsin gene in homozygous melanopsin knockout mice results in the loss of the intrinsic photosensitivity of the pRGC [129]. Loss of melanopsin, rod and cone function abolishes the pupil reflex response and photoentrainment [154]. Conversely, heterologous expression of melanopsin confers photosensitivity to previously nonphotosensitive cells [130, 131]. It has been suggested that melanopsin has bistability, i.e., that melanopsin can function both as a photopigment and as an isomerase for its own regeneration [120, 131, 132]. This is an important consideration for a photoreceptor located in the inner retina, as rod and cone photoreceptors in the



outer retina rely on the RPE to replenish their photopigment [121, 124].

There are approximately 3,000 such melanopsin-expressing RGCs in each human retina, accounting for 0.2–0.8% of the total 1,500,000 ganglion cells [153, 155]. Their concentration decreases from 20 to 25 cells/mm<sup>2</sup> in the parafoveal area to 3–5 cells/mm<sup>2</sup> more eccentrically. Sparsely spread, the melanopsin-expressing ganglion cell has the widest dendritic arbor of any ganglion cell in primates. Both rods and cones modify the activity of the melanopsin-expressing ganglion photoreceptor demonstrating that all three photoreceptor pathways interact to an extent in the primate retina.

Melanopsin-dependent photoreception is the earliest visual function detected in the mammalian retina [156] and becomes merged with the image-forming system [154, 155]. We have alluded above to its presence in the adult human [153, 154], but how much the melanopsin-based visual pathway contributes during development, as has been suggested [157], has not been established yet.

### 2.3.5 Targets of Retinal Projections

The axons of the retinal ganglion cells project to various subcortical regions of the brain [34, 158, 159]. The ganglion cell axons travel within the superficial retinal nerve fiber layer towards the optic disc where they become myelinated. In the optic tract, 90% of all ganglion axons terminate in the LGN, whence postsynaptic neurons project via the optic radiations to the ipsilateral visual cortex as part of the retino-geniculocortical pathway [110, 160–162]. The parasol and midget ganglion cells contribute to two parallel retinal projections to the brain: the smaller magnocellular pathway, which is formed by parasol cells and mostly concerned with luminance and motion detection, and the larger parvocellular pathway, which is formed by midget cells and concerned with color and high resolution [6, 33, 34, 42, 55, 110]. The retino-geniculocortical pathway is the largest visual pathway and serves conscious visual sensation. In addition, a number of phylogenetically older, but smaller and less well-understood ganglion cell tracts are found in the optic tract which are not involved in conscious vision, including

the tracts to the hypothalamus, the pretectal nucleus, the superior colliculus, the pulvinar nucleus of the thalamus, the accessory optic system, and the reticular formation [34, 153, 155, 158, 159, 163].

## 2.4 Retinal Development

The complex neuronal cytoarchitecture and neurophysiology of the mature retina are not completed at birth and take several years to develop. The embryology of the human eye and the retina is described in this book and elsewhere [1–5, 75, 164].

Human and monkey studies have provided more insight into the mechanism of retinal development. Cellular proliferation expands retinal tissue mass. Labeling experiments in rodents have shown that retinal stem cells are capable of producing all retinal neuron cell types and Müller cells [165]. Thymidine birthdating of retinal cells in the monkey demonstrates that retinal cell type differentiation is sequential: The ganglion, horizontal, and cone photoreceptor cells are the first cell types to differentiate, followed by the amacrine cells, the bipolar, and the rod photoreceptor cells [166]. The mechanisms regulating the differentiation of the pluripotent retinal stem cell into a particular cell type are not fully understood [167, 168].

Retinal development begins centrally before extending peripherally, i.e., a rudimentary macula is formed first followed by peripheral retina. Subsequent expansion of the peripheral retina accounts for most of the eye's axial growth. At the same time, the retina matures in a centripetal direction, i.e., the peripheral retina is fully developed long before the posterior pole is. Thus, the fovea is immature at birth and undergoes maturational changes for several years [169].

### 2.4.1 Eye Growth and the Expansion of the Peripheral Retina

The sagittal length of the human eye varies between 16 and 18 mm at term [170–173]. Eye growth is most rapid between the eighth and the fourteenth fetal week [174]. In utero, the sagittal length is about 12 mm at 6 months gestation, 14.4 mm at 7 months gestation, and

16.8 mm at 8 months gestation [170, 175]. Therefore, the eye reaches approximately half the adult size (24 mm) at six fetal months and two thirds of the adult size by term. After birth, axial growth increases by another 3.5 mm in the first 18 months, by 1 mm/year till the age of 3–4 years, and by only 0.1 mm/year after that till the age of 14–15 years [170]. The retinal surface expands by 6.6-fold between 14 and 40 fetal weeks [164] and by another 1.8-fold (from 0.5 to 0.9 cm<sup>2</sup>) between birth and 6 years of age in humans [176]. Perhaps, retinal stretch is a more appropriate term as any increase in surface area is not accompanied by an increase in neural cellular content.

Careful measurements have shown that most of the axial eye growth is due to the growth of the peripheral section of the posterior segment [6, 11, 177]. The centralmost 16–20° of the retina are not thought to grow after the twelfth fetal week [12]. In vivo, digital imaging of the neonatal retina has permitted study of postnatal retinal development, and the findings confirm that while the optic nerve diameter increases some 50% after birth to adulthood [178, 179], during this same period there is only an 11% increase in optic disc-fovea distance, supporting the concept that most growth of the eyeball occurs in the equatorial region while the visually critical part of the retina is relatively unperturbed during development (Table 2.1) [179]. Axial growth and the growth of the vitreous cavity, but not the deepening of the anterior chamber, are influenced by sex and are greater among male than among female infants [171].

## 2.4.2 Foveal Development

Although a rudimentary macula is formed very early during ontogenesis, the macula takes much longer than the peripheral retina to mature histologically and functionally. Isenberg [178] described a clinical staging system (stages 1–5) for early macular development based on three readily observable ophthalmoscopic features: the presence or absence of macular pigmentation, the annular reflex, and the foveolar reflex. He reported that the process of macular pigmentation began at 34 weeks and gave rise to an annular and foveolar reflex by 42 weeks of gestational age. It is thought that increased pigmentation reflects changes in the RPE layer and probably is due to an increase in density and thickness of the RPE cells in the region of the macula [179], while the development of the annular and foveolar reflexes reflect the structural maturation of the macula and the foveola [169].

The earliest sign of the developing macula is a central area of thickening, which forms an elevation on the retinal surface [75]. This is due to the presence of up to nine rows of ganglion cells in the macular region. Foveal formation involves two major neuronal migrations that take place in opposite directions: the peripheral displacement of inner nuclear and ganglion cells and the central migration of red and green cone photoreceptor cells [11, 12]. The outwards migration of the cells of the inner nuclear and ganglion layer results in gradual central foveal thinning and the formation of the foveal pit and continues for years in children. At

**Table 2.1** Summary of Optic Disk Measurements in Infants

Investigators	Type of study	Age at examination	Horizontal disc diameter (mm)	Vertical disc diameter (mm)	Mean optic disc area (mm <sup>2</sup> )	Optic disc-fovea distance (mm)
Rimmer et al. [93]	Postmortem	<40 weeks gestation	0.93 ± 15	1.10 ± 21	0.82 ± 0.26	
McLoone et al. [180]	In vivo digital imaging	33–34 weeks postmenstrual age	1.05 (mean)	–	1.13 (mean)	–
De Silva et al. [181]	In vivo digital imaging	32–49 weeks postmenstrual age	1.05 ± 13	1.41 ± 19	1.17 ± 26	4.4 ± 4

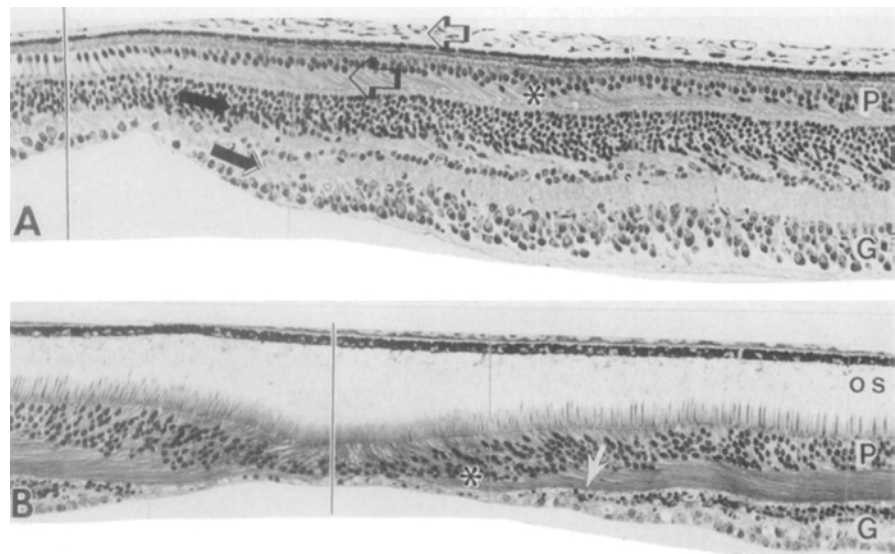
the same time, the cone photoreceptor cells migrate towards the foveola. As a result, the area of the human rod-free zone decreases from 2.00 mm<sup>2</sup> at 22 fetal weeks to less than 0.40 mm<sup>2</sup> at 45 months. The contraction of the rod-free zone coincides with a steep increase in human cone density from 18,000 cones/mm<sup>2</sup> at 22 fetal weeks to 36,000 cones/mm<sup>2</sup> at 5 days, 108,000 cones/mm<sup>2</sup> at 45 months to 208,000 cones/mm<sup>2</sup> by adulthood [11, 33]. Microglial cells leave the foveola, while the immigration of astrocytes and endothelial cells is inhibited [41] (Fig. 2.7).

The foveolar cones predominantly innervate ON- and OFF-midget bipolar cells (and indirectly ON- and OFF midget ganglion cells) with little or no convergence [41]. Foveal maturation is marked by changes in cone morphology as well. Peripheral cones mature long before foveal cones do. At birth, foveolar cones are still short and stubby with a rudimentary outer segment. Within the first year of life, the axonal fibers, the inner and the outer segments, all narrow and elongate. The length of the outer segments, for instance, increases 7 times within the first 15 months of life and twice more by adulthood. At the same time, the diameter of the inner segment decreases from 6 to 2  $\mu$ m between birth and adulthood allowing many more and longer

cones to be densely packed into the central fovea. Because the cone pedicles remain attached to the horizontal and bipolar cells, their outward movement leads to the gradual elongation of the outer fibers and the formation of Henle's layer. Though the human ganglion cell layer starts to thin from 14 fetal weeks, the human fovea still contains one to two layers of ganglion cells as well as most of the inner nuclear layer at birth. As a result, the human fovea does not achieve a more mature appearance till 11–15 months and still has only half of its adult foveal cone density at the age of 4–5 years, reflecting the long duration of postnatal foveal maturation (Fig. 2.8).

The sophisticated neuronal cytoarchitecture and neurophysiology of the retina provide the basis for mature visual function. However, the creation of this complex structure takes time and is carefully controlled by a developmental process of structural and functional maturation, which is not complete until several years after birth. The complexity and the length of the process of development make the developing visual system particularly vulnerable to the effects of genetic and environmental interference. The effects of this interference, and the pathology this generates, are the subject of the subsequent chapters.

**Fig. 2.7** Sections of the newborn (a) and adult (b) retina. Vertical line marks the foveal center. *Open and close arrows* indicate retinal layers where central and peripheral migration occur respectively. The *white arrow* in (b) marks the centralmost neurons. *P* photoreceptors; *G* ganglion cell layer. The *asterisk* marks the centralmost rods in the adult and newborn retina and indicates that some central migration has taken place during development. Reproduced with permission from Hendrickson 1994 [12]



**Fig. 2.8** Artist's conception of the perceptual appearance of a visual scene for infants of different ages. (a) Newborn, (b) 1 month, (c) 2 months, (d) 3 months, (e) 6 months, (f) adult. (copyright by Tony Young; used with permission)[182]





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