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Anatomy of the Human Optic Nerve: Structure and Function

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Abstract

The optic nerve (ON) is constituted by the axons of the retinal ganglion cells (RGCs). These axons are distributed in an organized pattern from the soma of the RGC to the lateral geniculated nucleus (where most of the neurons synapse). The key points of the ON are the optic nerve head and chiasm. This chapter will include a detailed and updated review of the ON different parts: RGC axons, glial cells, connective tissue of the lamina cribrosa and the septum and the blood vessels derivate from the central retina artery and from the ciliary system. There will be an up-to-date description about the superficial nerve fibre layer, including their organization, and about prelaminar, laminar and retrolaminar regions, emphasizing the axoplasmic flow, glial barriers, biomechanics of the lamina cribrosa and the role of the macro- and microglia in their working.

Keywords: optic nerve, lamina cribrosa, prelaminar region, retrolaminar region, vascularization, glioarchitecture, blood barrier

1. Introduction

The retina and the optic nerve constitute the beginning of the visual pathway. The visual pathway is made up, in addition to the retina and optic nerves (ON), of the optic chiasma, optic tracts, lateral geniculate nucleus (LGN), optic radiations and visual cortex. There are other areas of the cortex also associated with vision such as the frontal eye fields [1–4].

1.1. Retina

Apart from the cells of association (the horizontal cells and amacrine cells) and glial cells (the Müller cells, astrocytes and microglia), the retina is composed of three superimposed neurons that establish a connection with each other. The external neuron is the photoreceptor. The second neuron, the bipolar cell, is in the nuclear layer. The third or internal neuron is the ganglion cell (GC) [1]. The cell bodies of most of the GCs are located in the ganglion cell layer (GCL), between the retinal nerve fibre layer (NFL) and the inner plexiform layer [2]. Their axons form the retinal NFL and synapse with neurons in the LGN of the thalamus [1, 2]. There are up to seven layers of GC bodies in the central retina or fovea (60–80 μm thickness) and a few as one cell layer in the peripheral retina (10–20 μm) [2]. There are between 500.000 and 1.2 million GCs per retina [1, 4] and approximately 100 rods and 4–6 cones per GC [2].

The axons form criss-crossed bundles but are separated and ensheathed by glial cells [1, 2]. The bundles leave the eye to form the optic nerve (ON). Upon existing through the lamina cribrosa, the axons become myelinated with oligodendrocytes [1, 2].

The visual field (VF) and the retina have an inverted and reversed relationship. The upper VF falls on the inferior retina (below the fovea), lower VF on the superior retina, nasal VF on the temporal retina and temporal VF on the nasal retina [3].

One of the most commonly used diagnostic tests in ophthalmology is the optic coherence tomography (OCT). This test analyses the ganglion cell complex (GCC) which represents the combination of three layers: the NFL, GCL and inner plexiform layer. These layers contain, respectively, the axons, the cell bodies and the dendrites of the ganglion cells.

1.2. Optic nerve

The ON is formed by the convergence of GC axons at the optic disc or papilla. In the papilla there are no photoreceptors, and it represents the blind spot [1]. Foveal/macular fibres constitute around 90% of all axons leaving the eye and forming the papillomacular bundle [2].

The optic nerve has some characteristics that make it unique. It is the only tract in the central nervous system (CNS) to leave the cranial cavity and the only one that can be visualized clinically. It is subdivided into fascicles by connective tissue and glial septa, and it is surrounded by cerebrospinal fluid [2].

The ON can be divided into four main portions (**Figure 1**):

- Intraocular nerve head (1 mm in length) (**Figures 2** and **3A**)

It extends from the surface of the optic disc to the posterior margins of the sclera. The nerve fibres are not myelinated in this portion. Myelination commences approximately with the termination of the subarachnoid space at the posterior limits of lamina cribrosa [1, 2] (**Figures 3F1** and **F2**).
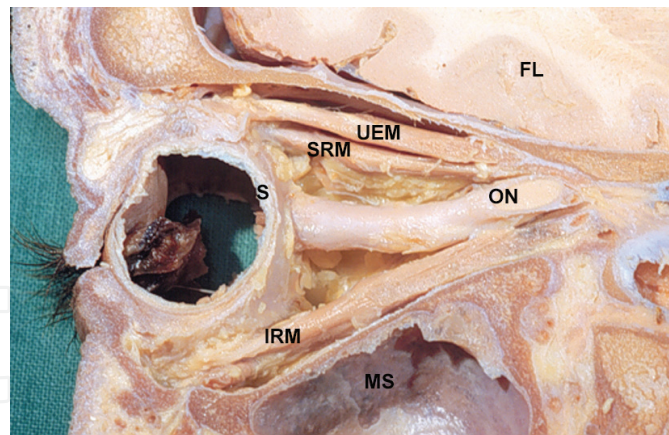
- Intraorbital (25–30 mm)

Figure 1. Human optic nerve. Parasagittal cut at the level of the orbit. The intraorbital path of the optic nerve (ON), surrounded by the retrobulbar fat and the extrinsic eye muscles, is observed (FL, frontal lobe; IRM, inferior rectus muscle; MS, maxillary sinus; S, sclera; SRM, superior rectus muscle; UEM, upper eyelid muscle). *Provided by Mérida JR from Desarrollo del nervio Optico in Neuropatias ópticas diagnóstico y tratamiento. Industria Grafica Mae Spain, 2002, p13.*
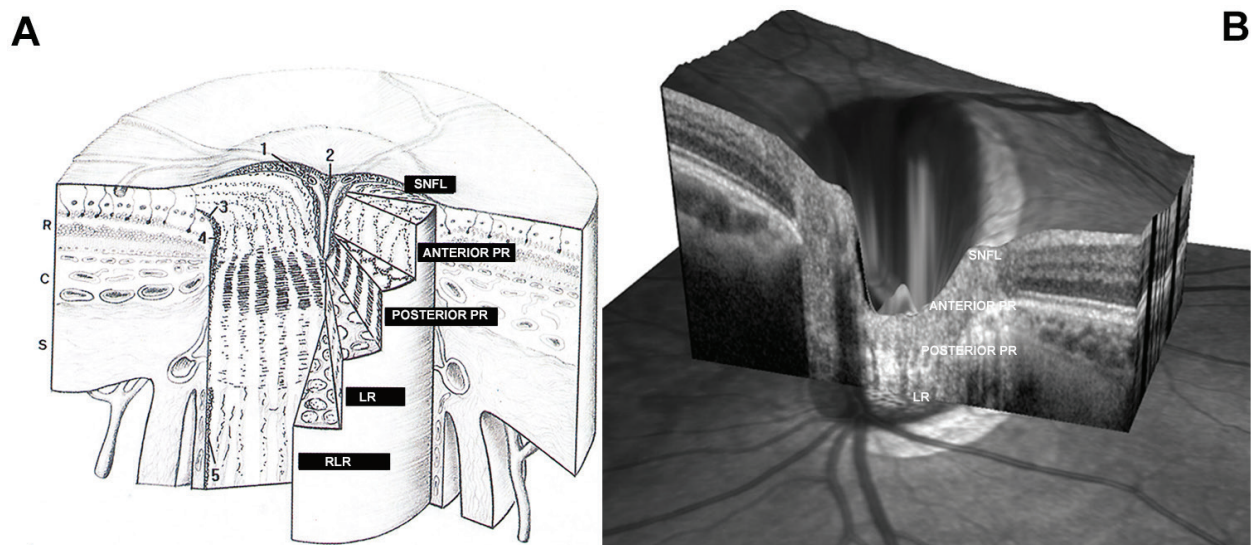

Figure 2. Optic nerve head (ONH). (A) Three-dimensional scheme of the optic nerve head (ONH) regions. (1) Elschnig internal limiting membrane, (2) Kuhnt central meniscus, (3) Kuhnt intermediary tissue, (4) Jacoby tissue, and (5) peripheral glial mantle of Graefe. (B) 3D map of ONH with spectral domain OCT Heidelberg [superficial nerve fibre layer (SNFL); prelaminar region (PR); laminar region (LR); retrolaminar region (RLR)] ((A) modified with permission from Triviño et al. [29]).

This portion extends backwards and medially from the back of the eye to the optic canal in the sphenoid at the apex of the orbit. It is covered by three layers of meninges: the pia, the arachnoid and the dura mater [1, 2] (**Figure 9A**). The central retinal vessels must cross the subarachnoid space (between the pia and the arachnoid) and are therefore vulnerable, particularly the vein, in cases of raised intracranial pressure [2].

The intraorbital portion of the ON has a slight S-shaped bend, which allows a full range of ocular movement without stretching the nerve [1, 2]. As the ON approaches the orbital apex,
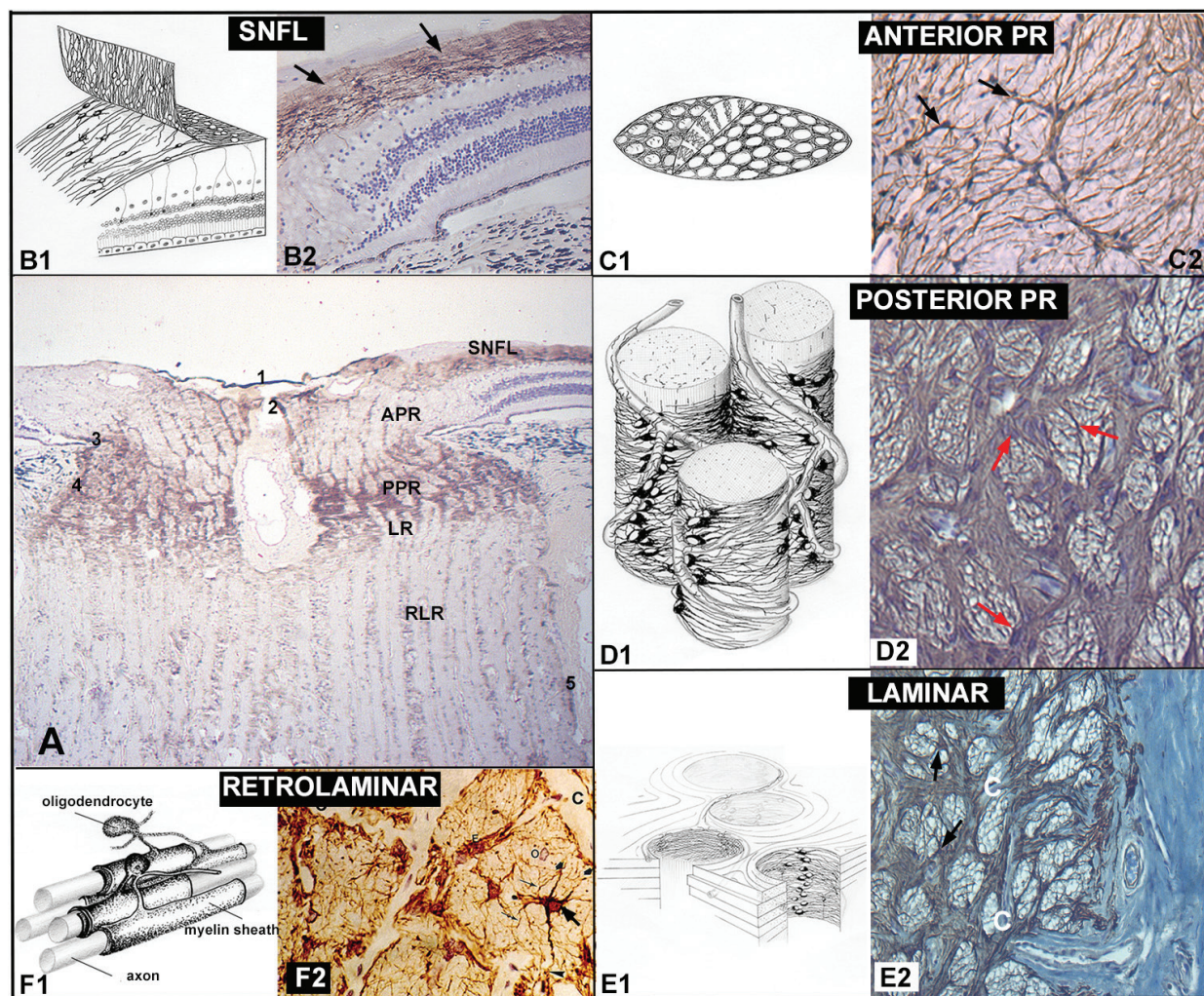
Figure 3. Morphology and distribution of astrocytes of the human optic nerve (O. N.). (A) Histological section of ON head. Superficial nerve fibre layer (SNFL), anterior prelaminar region (APR), posterior prelaminar region (PPR), laminar region (LR), and retrolaminar region (RLR). (1) Elschnig internal limiting membrane, (2) Kuhnt central meniscus, (3) Kuhnt intermediary tissue, (4) Jacoby tissue, and (5) peripheral glial mantle of Graefe. (B) Superficial nerve fibre layer: (B1) three-dimensional scheme and (B2) histological section. (C) Anterior prelaminar region: (C1) three-dimensional scheme and (C2) glioarchitecture. (D) Posterior prelaminar region: (D1) a three-dimensional diagram of the glial tubes and (D2) glioarchitecture. (E) Laminar region: (E1) three-dimensional scheme with pores covered with astroglia and (E2) histological section. (F) Retrolaminar region: (F1) scheme of myelin sheath forming by oligodendrocytes and (F2) histological section [astrocytes (arrows), collagen (C), oligodendrocytes (O), vessels (v)]. PAP immunohistochemistry: GFAP-PAP-haematoxylin (A, B2, F2) and GFAP Calleja's stain (C2, D2, E2) (B1,C1,C2,D1,F2,E1; modified with permission from Triviño et al. [29]).

it is surrounded by the tendinous annulus of Zinn, which has its origin in the rectus muscles [2, 4] (**Figure 1**).

- Intracanalicular (4–10 mm)

The intracanalicular portion of the ON passes through the optic canal, accompanied by the ophthalmic artery and the sympathetic nerves [2].

- Intracranial portion (10 mm)

The optic nerves leave the cranial end of the optic canal and pass medially, backwards and slightly upwards within the subarachnoid space of the middle cranial fossa [2]. They end by forming the optic chiasma in the floor of the third ventricle [1, 2].

The visual field (VF) can detect the alterations in nerve fibres [3]. The alterations of the different main bundles cause the following defects:

- In the papillomacular bundle (macular fibres that enter the temporal area of the disc): the central scotoma, the centrocecal scotoma and the paracentral scotoma

- In the arcuate nerve fibre bundle (fibres from the temporal retina to the disc that enters to disc in the superior and inferior poles): the arcuate Bjerrum's scotoma, Seidel's scotoma, the nasal step and the isolated scotoma within arcuate area

- In the nasal nerve fibre bundle (fibres that enter the nasal area of the disc in non-arcuate fashion, 'straight'): wedge-shaped temporal scotoma arising from the blind spot and does not necessarily respect the temporal horizontal meridian

The analysis of retinal axons using OCT allows us to detect axonal loss in vivo. The OCT technique and scanning laser polarimetry with variable corneal compensation (GDx, Carl Zeiss Meditec) are used to measure retinal nerve fibre layer (RNFL) thickness. The peripapillary RNFL has the advantage that the axons are unmyelinated, and any change is not confounded by demyelination as is the case of the optic nerve itself. Thinning of the peripapillary RNFL has been detected in patients with glaucoma, optic neuritis, multiple sclerosis, neuromyelitis optica, Alzheimer disease, Parkinson disease and other diseases. However, the patterns of change differ in some aspects.

1.3. The optic chiasma

It is situated at the junction of the anterior wall and the floor of the third ventricle [1], approximately 5–10 mm above the diaphragma sellae and the hypophysis cerebri [2]. Fifty-five percent of ON fibres cross in the chiasm [4]. This partial crossing of ON fibres is an essential requirement for binocular vision [2]. The fibres from the nasal hemiretina of each eye cross the midline to enter the contralateral optic tract after taking a short loop in the ipsilateral tract or into the contralateral optic nerve. Nerve fibres from the temporal hemiretina do not cross at the chiasma [2]. Macular fibres run posteriorly and centrally [3, 4]. Nasal fibres of the ipsilateral eye cross the chiasma and join the uncrossed temporal fibres of the contralateral eye [3]. Lower retina fibres lie laterally in the tracts and upper retinal fibres will lie medially.

Inferonasal retinal fibres cross into the chiasm anteriorly, approximately 4 mm into the contralateral ON, before running posteriorly forming 'Willebrand's knee' [3, 4].

The lesion of the nervous fibres at the level of chiasma, recorded by a VF, produces a bitemporal hemianopia due to the interruption of decussating nasal fibres [3]. When 'Willebrand's knee' is affected, it produces junctional scotoma [3, 4].

Using the OCT technique, diverse patterns of GCC loss in patients with chiasmal compression have been described. In addition, binasal GCC loss was typical and could be seen with minimal or no detectable VF loss. Moreover, thinning of the GCC may be detected before loss of the RNFL in some patients. After chiasmal decompression, the majority of patients showed an improvement in VF despite persistent GCC loss. Patients with less GCC loss before decompression had better postoperative VF.

1.4. The optic tracts

The optic tracts wind around the cerebral peduncles of the rostral midbrain, and they each divide into two roots. The first one is a large lateral root, which terminates posteriorly in the LGN and is related with a conscious visual sensation. The second one is a smaller medial root, which is connected both to the pretectal area and to the superior colliculus by the superior brachium and carries around 10% of tract fibres. This medial root functionally is not concerned with conscious vision [1, 2].

Lower retinal fibres and their projections lie in the lateral portion of the optic tract and terminate in the inferior striate cortex on the lower bank of the calcarine fissure. Upper retinal fibres project through the medial optic tract and ultimately terminate in the superior striate cortex [3].

The lateral root of the optic tract passes backwards, a little upwards, and terminates in the LGN, a part of the thalamus (a relay station for ascending sensory information). There is a 90° rotation (90° inward twist) of fibres from the nerves through the chiasm into the tracts (4) as it passes around the cerebral peduncles [2]. Macular fibres run centrally [1].

Damage to optic tract results in contralateral relative afferent pupillary defect (RAPD) because 55% of fibres cross [3, 4].

Optic tract lesion is an uncommon clinical entity. The primary characteristic is a homonymous VF defect that may be complete or incomplete. When the defect is incomplete, there is relative incongruity. When it is complete, there is an associated contralateral RAPD. Visual acuity and colour vision are preserved; unless there is bilateral involvement or anterior extension to involve the optic nerve or chiasm. When duration is enough, the contralateral fundus demonstrates a band or 'bow tie' atrophy of the disc and NFL.

The VF can detect alterations of the optic tract such as incongruous homonymous hemianopia (nerve fibres of corresponding points do not yet lie adjacent to one another). All retrochiasmatic lesions result in a contralateral homonymous hemianopia on the opposite side of the lesion. In general, the more posterior (towards the occipital cortex) the lesion is in postchiasmal visual pathways, the more likely the defects will be congruous [3].

1.5. Lateral geniculate nucleus (LGN)

Each LGN is distinguishable on the surface of the brain as an ovoid projection on the postero-inferior aspect of the thalamus, partly obscured by the overhanging temporal lobe [1, 2]. It consists of a body, head, spur and hilum. The hilum is continuous with the groove between the medial and lateral roots of the optic tract, which enters its anterior aspect. It lies at the anterior aspect of the pulvinar, which also partly surrounds it, particularly from above. Macular vision is subserved by the hilum and peripheral field by the medial and lateral horns [3].

The analysis by OCT shows that an uncrossed, temporal projection of the nerve fibre is affected in the eye ipsilateral to the damaged optic tract, resulting in preferential atrophy of the superior and inferior parts of the optic disc rim. In contrast, the crossed, nasal projection of the nerve fibres is damaged by the lesion in the contralateral eye, leading to the preferential atrophy of temporal and nasal parts of the optic disc rim, which is denoted as band atrophy.

In addition, Kanamori et al. [5] described reduced RNFL values in the contralateral eyes, the temporal and nasal (horizontal) by OCT. In contrast, the superior and inferior (vertical) RNFL were preferentially reduced compared to the horizontal RNFL, which are both located in the ipsilateral eyes. In the RNFL temporal-superior-nasal-inferior-temporal (TSNIT) profiles, a so-called double hump pattern, which represents thicker RNFL in the superior and inferior quadrants and thinner RNFL in the temporal and nasal quadrants, was preserved in the contralateral eyes but lost in the ipsilateral eyes. The analysis of the GCC using RTVue-OCT showed characteristic patterns of GCC thinning in both eyes, which is compatible with optic tract syndrome (OTS). The contralateral eyes showed an apparent GCC reduction from the nasal area to the fovea, whereas the ipsilateral eyes exhibited a significant GCC reduction from the temporal area to the fovea. GCC analysis provides information about the inner macular architecture. In this study, all cases exhibited marked changes in the GCC that were compatible with OTS but no changes in RNFL thickness. The RNFL in the superior and inferior parts of the optic nerve is composed of retinal nerve fibres originating from both temporal and nasal hemiretinal areas. In contrast, GCC temporal to the fovea in the temporal hemiretina comprise strictly retinal ganglion cell elements that reside within the corresponding areas. Such enrichment in retinal ganglion cell components, as well as stringent retinotopic segregation, may render the GCC superior to the circumpapillary retinal nerve fibre layer (cpRNFL) in the detection of homonymous hemianopic atrophy [5].

The LGN in which the great majority of the optic tract fibres terminate has a complex structure: it consists of six laminae or cell layers (numbered 1 to 6 beginning at the hilum), oriented in a dome-shaped mound similar to a stack of hats. Nerve fibres derived from the contralateral eye (crossed fibres from the nasal half of the retina) terminate on cell bodies in layers 1, 4 and 6. Those of the ipsilateral eye (uncrossed) terminate in layers 2, 3 and 5 [2, 4]. Thus, each LGN receives information from both retinae. Each retinal ganglion cell axon may terminate on up to six geniculate cells; however, these are located in one lamina. Fibres from the upper quadrants of peripheral retinae synapse on the medial aspect of the LGN and those of the lower quadrant on the lateral aspect. The macula projects to a disproportionately large central wedge of the LGN [2, 3]. Layers of LGN can also be categorized by neuronal size [4]:

- Magnocellular neurons (M cells): layers 1 and 2. These layers receive inputs from magnocellular RGCs. Magnocellular pathway is implicated in motion detection, stereoacuity and contrast sensitivity.

- Parvocellular neurons (P cells): layers 3 and 6. These layers receive inputs from parvocellular RGCs. Parvocellular pathway is implicated in fine spatial resolution and colour vision.

- Koniocellular neurons (K cells): These cells are located in interlaminar zones and superficial layers, receive inputs from both retinas and the superior colliculus and may modulate information.

The posterior aspect of the LGN is dome shaped, and it is from here that the geniculate cell axons form the optic radiation emerge [1, 2, 4]. The bulk of the LGN sends its fibres via the optic radiation to the visual cortex (area 17). The LGN has input from areas 17, 18 and 19, oculomotor centres and the reticular formation [2].

The alterations in the LGN, which are detected by the VF are [3]:

- Incongruous homonymous hemianopia

- Unique sector and sector-sparing defects due to a dual blood supply of LGN from anterior and posterior choroidal arteries

1.6. Postgeniculate pathway

1.6.1. Optic radiation

Optical radiation fibres show a certain order: the most anterior ones come from the lower part of the retina (upper VF) and the most posterior and dorsal ones from the upper part of the retina (lower VF) [1]. In the temporal lobe, fibres of the inferior retina are distributed as follows: the fibres of the inferotemporal part come from the ipsilateral eye, and the fibres of the inferior-nasal part are from the contralateral eye. They move anteriorly from the LGN and travel around ventricular system into the temporal lobe (Meyer's loop) [3, 4]. Inferior macular fibres do not cross as far anteriorly in the temporal lobe [3]. In the parietal lobe, fibres of the superior retina are distributed as follows: the superotemporal fibres come from the ipsilateral eye and the superonasal from the contralateral eye. They travel superiorly in the optic radiation, in white matter from the parietal cortex to the occipital lobe [3, 4]. Macular fibres travel more centrally [4].

The alterations of this pathway detected by VF are:

- Anterior temporal lobe lesions produce midperipheral and peripheral contralateral homonymous superior quadrantanopia ('pie in the sky' field defect); more extensive temporal lobe lesions may cause defects that extend to the inferior quadrants but 'denser' superiorly [3].

- Parietal lobe lesions tend to affect superior fibres first, resulting in contralateral inferior homonymous quadrantanopia or a homonymous hemianopia 'denser' inferiorly [3].

- The injury of a complete optic tract interrupts the fibres coming from the temporal half of one retina and of the nasal half the other, causing blindness in the right or left halves of both retinas. Whether the right or the left band is affected, it produces a homonymous hemianopia on the side contralateral to the affected band 1.

1.6.2. Primary visual cortex or Brodmann area 17

The central (30°) visual field occupies a disproportionately large area (68–83%) of the visual cortex [3]. The vertical meridians are represented along the border of the calcarine lips, while the horizontal meridian follows the contour of the base of the calcarine fissure [3].

Main defect types observed by the analysis of VF are the central homonymous hemianopia with or without macular sparing depending on the location of the lesion [3].

Using the OCT technique, it has been described that acquired unilateral damage to the occipital lobe resulting in homonymous hemianopia leads to nerve fibre layer thinning. Thinning

of the GCL on the lesion's projecting sector of the macula has been described in lesions in the posterior visual pathway with a strong correlation between the corresponding macular segment of the GCL and the VF. In addition, the finding of sector macular GCL atrophy proves retrograde trans-synaptic degeneration of neurons in the visual pathway in cases without other ophthalmic or neurological diseases. It has been proposed that this is probably because at the macula, the bodies of the neurons are more numerous and topographically organized to correspond to the VF. In contrast, the anatomical distribution of fibres in the peripapillary RNFL is more complex, making a correlation with the visual field more difficult to establish. Another important element is the absence of blood vessels or other structures that may interfere with the OCT image acquisition. It is noteworthy that cases with macular sparing hemi- and quadrantanopia also showed macular GCL atrophy away from the fovea. It is perhaps explained the representation of a 15–20u of visual field in the area scanned by the OCT instrument used and the absence of ganglion cells on the fovea.

2. Microscopic anatomy and function of the optic nerve

The components of the optic nerve are:

- The axons of the RGCs

- Glial cells: astrocytes, oligodendrocytes and microglia

- The connective tissue: which constitutes the lamina cribrosa and the septa that fasciculate the optic nerve

- Blood vessels, derived from both the central retinal artery (CRA) system and the ciliary system

The intraocular nerve head can be divided into four parts (**Figure 2**):

- The superficial nerve fibre layer (**Figures 3A**, **B1** and **B2**)

- The prelaminar region (**Figures 3A**, **C1**, **C2**, **D1** and **D2**)

- The laminar region (**Figures 3A**, **E1** and **E2**)

- The retrolaminar region (which corresponds to the anterior portion of the intraorbital region) (**Figures 3A**, **F1** and **F2**)

The basic organization of the optic nerve head is similar in all regions. The axons of the RGCs form beams of several thousand axons each, which are surrounded by different tissues; the latter, however, are those that will vary in the different areas of the nerve.

2.1. Superficial nerve fibre layer

In the retina, the axons of the RGCs will converge towards the optic disc following a fairly straight trajectory, thus constituting the superficial nerve fibre layer (**Figures 3B1** and **B2**).

This layer is constituted by axonal bundles that are formed by the gathering of rows of axons that converge on their way to the optic disc. Therefore, an axonal bundle that reaches the optic nerve head will contain axons from RGCs, the location of which varies from the peripheral retina to the vicinity of the head of the optic nerve [6]. In addition, another characteristic of the axons of this region is where they are unmyelinated because there are no oligodendrocytes. The majority of glial type of this layer is made up of astrocytes (**Figure 3B1** and **B2**) [7].

The axons of the RGCs follow an established pattern. In addition, the presence of fovea in the human retina will affect the arrangement of the axons in this layer in such a way that the axons of the RGCs on the nasal side, both superior and inferior, are not affected by the fovea and go directly to the optic disc. The same thing happens with the RGCs of the nasal temporal retina to the fovea, the axons of which form the papillomacular bundle on their way to the optic disc [6]. However, the RGCs temporal to the fovea cannot go through this area to join the papillomacular bundle. Therefore, they surround the fovea forming arcs above and below it, as they go towards the optic disc (arcuate bundles). Temporal to the fovea, there is a dividing line (the horizontal raphe) which separates the RGCs, whose axons are going to pass over the fovea, from the RGCs, and whose axons are going below this line [6, 8–10].

With respect to the organization of the axons in the thickness of this layer, different theories have been postulated. Some propose that the axons of the RGCs located more peripherally are arranged closer to the GCL, while the axons closest to the optic nerve head go through the superficial NFL perpendicularly so as to arrange themselves close to the vitreous surface. Thus, the axons coming from the periphery, which are close to the GCL, rotate 90° in the margin of the optic disc, whereas the axons of the more central RGCs go close to the vitreous surface and rotate close to the centre of the optic nerve head [11, 12]. However, other studies defend that the peripheral RGCs have the most superficial axons, while the most central ones have their axons close to the GCL. Therefore, at the optic nerve head, the most peripheral axons that run close to the vitreous surface rotate 90° in the most peripheral part of the optic nerve, while the central axons rotate in the centre of the optic disc [13].

At present, it is believed that the organization of the superficial NFL in the vitreous-scleral thickness is not related to the axonal eccentricity but that the axons coming from CGRs of different areas are mixed in a wedge extending from the periphery to the centre of the optic nerve. As a result, the axons in this region would not be predetermined to establish a retino-topic order [14, 15].

With the recent advances in imaging technology using a spectral-domain, optical coherence tomography (SDOCt9), in particular the enhanced depth imaging (EDI) technique of SD OCT, quantitative assessment of the superficial NFL thickness is possible. Observations in the distribution of peripapillary choroid show that the inferior region of the optic nerve is the thickest in comparison with the other regions [16–19]. Some authors postulate the theory that both the vascular watershed zone and the embryogenic location of the optic fissure closure may be responsible [20]. One of the known reasons for the vulnerability of the lower region is that of the lamina cribrosa in the lower pole has large pores and thinner connective tissue and glial support for the retinal ganglion cell axons to pass [21–23]. Another speculation could be that the thinnest peripapillary choroid in the lower quadrant, which represents an area of lower blood supply, may predispose the lower region of the optic nerve to glaucomatous ischemic damage [24].

2.1.1. Axoplasmic flow

For axons grow and maintain their structural integrity, it is necessary that there be an intra-axonal particle movement known as the axoplasmic flow. This flow is bidirectional in such a way that the molecules are transported from the soma to the axon and from axon to the synapse or from the synapse to the soma [25]. This soma-synapse communication is important in the case of neurons with long axons such as RGCs in which the axon has to travel a long way to reach the LGN [26]. Although most of the cytoplasmic organelles involved in protein synthesis are found in the neuronal soma, axons have a certain capacity for synthesis. The transported molecules vary substantially from filamentous components of the axon and proteins to mitochondria, secretory granules or multivesicular bodies [27].

The axoplasmic flow can be divided into [25, 26]:

a. Orthograde or antegrade: the direction of movement is from soma to synapse. It is involved in axonal growth and maintenance of the synapse. Three subtypes can be differentiated:

   1. Fast: the driving speed ranges between 100 and 500 mm/day. Mainly, membranous cell structures, neurotransmitters, hydrolases and soluble materials of low molecular weight are transported.

   2. Intermediate: the driving speed oscillates between 5 and 50 mm/day.

   3. Slow: the driving speed oscillates between 0.5 and 3 mm/day. It constitutes 80% of the total protein flow and is responsible for the transport of soluble proteins that form the structure of the axon. This is how structural elements of1 the axon, soluble enzymes and proteins travel.

b. Retrograde: it goes from the axon to the cell body. It carries a driving speed of about 200 mm/day. This flow is responsible for transporting the cellular detritus resulting from axon metabolism, aged organelles, fragments and membrane proteins towards the lysosomal compartment of the neuronal soma for its degradation and reuse or its definitive disablement. Furthermore, the retrograde flow serves to inform the cell body of the state of the axon terminal.

When axoplasmic flow is blocked, axons undergo a series of damage that leads to oedema, necrosis and optic atrophy. This has been demonstrated experimentally after the induction of different pathologies such as glaucoma, ischemic optic neuropathy or papilledema due to intracranial hypertension [28] (**Figure 4A**).

2.1.2. Astroglia

Other main constituents of the optic nerve are the astrocytes. In the superficial NFL, astrocytes have a thin cell body and their processes run parallel to the RGC axons (**Figure 3B1** and **B2**) [29, 30]. Under normal conditions, astrocytes establish contact with retinal neurons, providing stability to neural tissue [31]. Physiological studies have highlighted the important functions performed by these cells in the optic nerve and other parts of the CNS. Thus, they
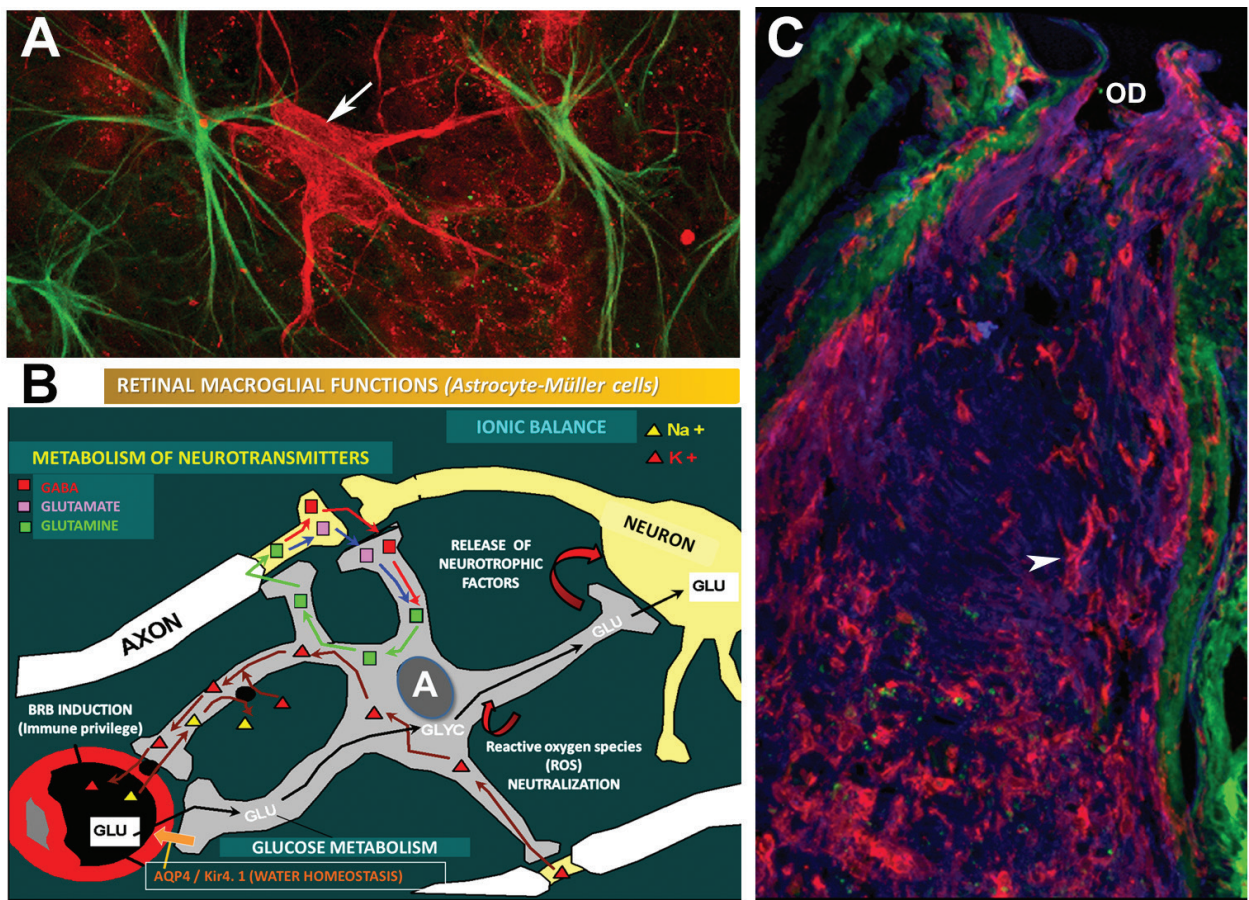
Figure 4. (A) Blockade of the axoplasmic flow. NF-200 (+) retinal ganglion cell in red (arrow), with an accumulation of neurofilaments in its cytoplasm by blocking its axoplasmic flow, in an experimental glaucoma model. In green, astrocytes GFAP(+). Retinal whole-mount immunofluorescence. (B) Scheme of the astroglia functions. (C) Microglia in the optic nerve. Iba-1+ ramified microglia (arrowhead) were observed. Immunofluorescence of the optic nerve section. Iba1+ in red and GFAP+ in blue. Optic disc (OD) ((A) modified with permission from Gallego et al. [73], (B) modified with permission from Ramírez et al. [181]).

are responsible for the storage of glycogen by providing glucose to the neurons. They regulate extracellular potassium levels. They play an important role in the regulation and metabolism of neurotransmitters such as GABA. They help in the elimination of retinal CO_2. They contribute to the maintenance of water homeostasis in the retina [27, 32–36]. Moreover, they are the inducers of the blood-retinal barrier properties (**Figure 4B**) [37]. At the level of the optic nerve, astrocytes are responsible for the fasciculation of axons [38, 39].

On the superficial NFL, there is a second morphological type of astrocytes, with a thick cell body and short processes. Its function is to separate and protect the optic nerve axons from the surrounding tissues, since they make up a series of glial limiting membranes:

a. Elschnig's limiting membrane (**Figures 3A** and **5A1**), which isolates the ganglion cell axons from the vitreous surface

b. The Kuhnt central meniscus (**Figures 3A** and **5A1**). Elschnig's limiting membrane is quite thick in the physiologic cup and constitutes this central meniscus. This is in continuity with glial tissue surrounding the adventitia of the central vessels (CRA and central retinal vein) [29, 30].

The main role attributed to these limiting glial membranes is to induce the blood-optic nerve barrier, which prevents the passage of molecules between the optic nerve and the adjacent tissues, which in this case is the vitreous body and the optic nerve vessels [30, 40].

2.1.3. Vascularization

The vessels that nourish the superficial NFL are dependent on the main retinal arterioles. The capillaries of this area continue along with the retinal peripapillary capillaries and the radial peripapillary capillary (RPC) network. Sometimes, there may be a vascular contribution from the prelaminar region by vessels derived from the ciliary system (**Figure 5A2**) [41–44].

The RPCs in the human retina were first described by Michaelson [45] as a unique plexus in their distribution to the posterior pole and seemed to be oriented parallel to the RNFL axons. Henkind [46] noted that the RPCs are the most superficial layer of capillaries lying in the inner part of the RNFL, and they run along the paths of the major superotemporal and inferotemporal vessels up to 4 to 5 mm from the optic nerve head (ONH). The RPCs have a distinctive and easily recognizable pattern of parallel, long, uniform-diameter vessels that remain within RNFL layers [47]. Henkind reported [46, 48] that in macaques and humans, RCPs are most prominent in the Bjerrum's region and are absent in the central macular region. RPCs have a long linear trajectory oriented parallel to the adjacent capillaries and radiate anteriorly from the ONH, forming only a few anastomoses with adjacent vessels [49]. In this region, retinal venous pulsations occur spontaneously in up to 95% of normal human eyes [50]. Some authors have identified that some major factors inherent to the retinal vein, as well as their relationship to surrounding optic disc structures, may influence some characteristics such as venous diameter, the presence of arteriovenous crossings and tissue depth, which affect sites of venous pulsation. Changes in venous compliance may affect venous pulsations in various retinal vascular diseases like diabetic retinopathy and venous occlusive disease, as well as glaucoma [51].

2.2. The prelaminar region

In the prelaminar region (PR), the axons of the CGRs change their trajectory, curving 90° to move towards the optic chiasm. This zone is also known as the choroidal region of the lamina cribrosa (**Figures 2** and **3A**) [41–44, 52].

In this region, two zones can be differentiated depending on the organization, arrangement, density and morphology of the astrocytes, as well as the way these cells fasciculate the axons. These two areas are the anterior PR (**Figures 3C1** and **C2**) and the posterior PR (**Figure 3D1** and **D2**) [29, 30].

2.2.1. Anterior prelaminar region

In the anterior PR, astrocytes are characterized by a stellate morphology with a thin cell body. Its disposition is closely related to the distribution pattern presented by the vascular system (**Figures 3C1**, **C2** and **5B2**) [30]. The vessels of this region derive from the ciliary system from the prechoriocapillary peripapillary choroid and can sometimes contribute to centripetal vessels from the circle of Zinn-Haller (**Figure 5B1** and **B2**) [8, 41, 44, 53, 54].
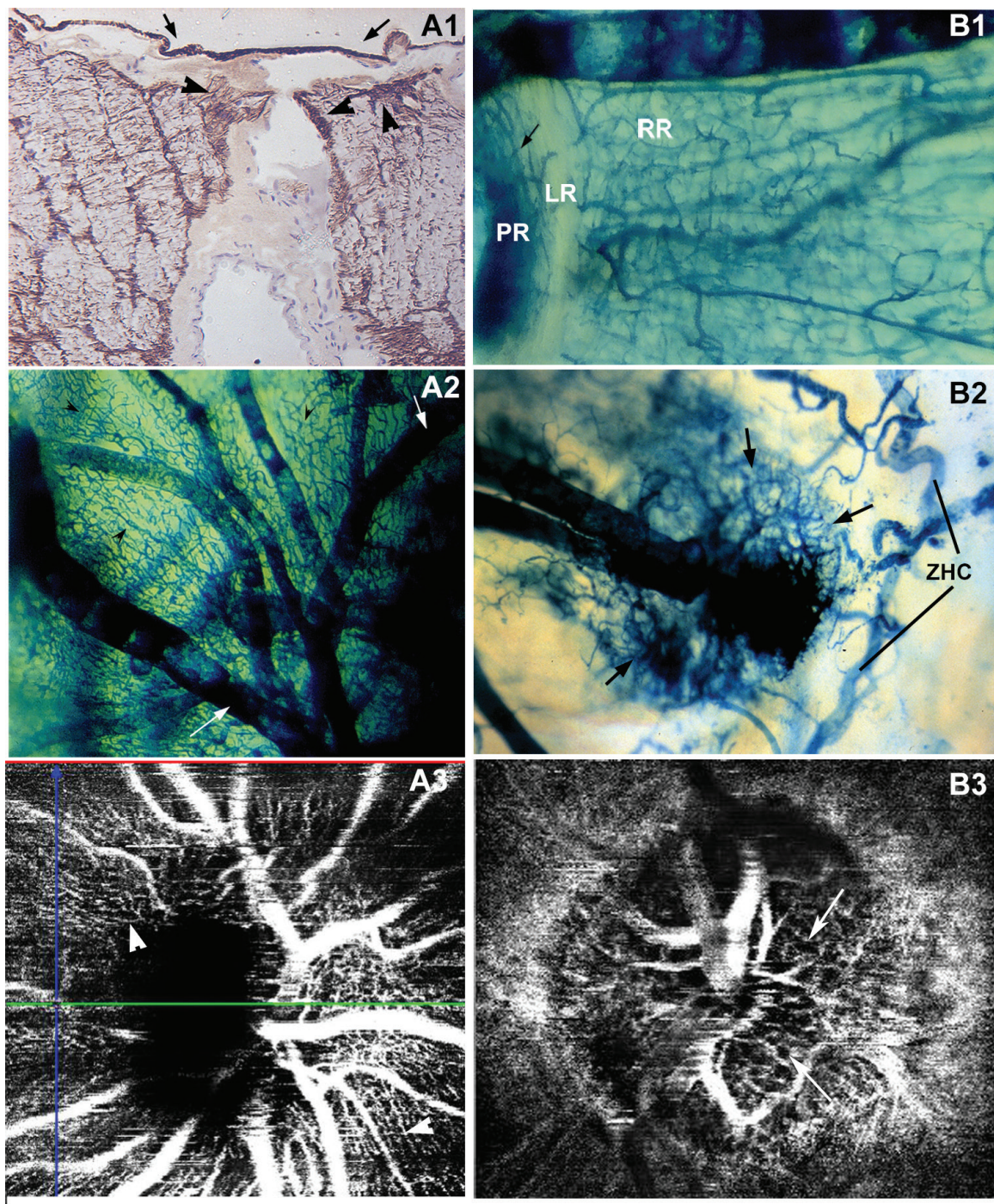
Figure 5. (A) Superficial nerve fibre layer (SNFL): (A1) Elschnig internal limiting membrane (arrows) and Kuhnt central meniscus (arrowhead). (A2) vascularization of the SNFL. Main branches of the artery and central vein of the retina (arrow) and capillary vascular bed (arrowhead). (A3) radial peripapillary capillaries (arrowhead). (B) Prelaminar region of the optic nerve head (ONH). (B1) lateral view of the vascularization of the ONH. Prelaminar region (PR), laminar region (LR), and retrolaminar region (RR). (B2, B3) vascularization of the prelaminar region (arrows). Zinn-Haller circle (CZH) ((A1) immunohistochemistry GFAP-PAP-Ünna Tanzer; (A2, B1, B2) diaphanization technique and vascular filling with polymers. (A3, B3) SD angio OCT Heidelberg).

Thin-bodied stellate astrocytes are the predominant cells in this region. Their cell bodies are basically positioned over blood vessels and emit primary processes in the direction of the vessel walls to make up an astroglial net that form a basket-like structure through whose

compartments the axons pass (**Figure 3A**, **C1** and **C2**) [30]. The layout of the astrocytes at this level reflects their supporting and protective function with respect to the myelinated fibres at the place in which they bend 90 degrees. These astrocytes may also have an important mechanical role as they could impede possible squeezing and rubbing among the nerve axons. This structure is relatively elastic if it is compared with the rigidity of the scleral lamina cribrosa. This elasticity may ameliorate or prevent irreparable nerve fibre damage when the disc swells from papilledema or neuritis [30].

2.2.2. Posterior prelaminar region

The basket-like structure of the anterior PR is substituted in the posterior PR by glial tubes (**Figure 3A**, **D1** and **D2**). The astrocytes of this region have thick bodies and form glial tubes through which the axons run. The blood vessels will be arranged between the thick glia partitions that make up the walls of these tubes (**Figures 3D1** and **D2**) [29, 30]. As in the anterior PR, these cells make up a structure through which the vessels that penetrate the nerve from the adjacent choroid run and form a pericapillary net with an irregular morphology. These glial tubes may have the mechanical function of resisting the pressures that originate at this level when the eyes move. The tubes surround the nerve fibres like a sheath. A number of data seem to support this glial function in the posterior PR: first, the abundance of GFAP supplies the astroglial processes with some tensile strength [55]. Thus, the richness of GFA protein observed in electron microscopy in the astroglial cells of this area would be providing a certain tensional force to the astroglial extensions [29, 30, 52, 56], and second, the presence of desmosomes [57] and gap junctions [58] supports this possibility. Both types of junction may have an important role in maintaining the astroglial net through which the axons pass, since even under high osmotic pressures the gap junctions remain intact. In addition, these glial tubes are organizing the axonal bundles preparing them for entry into the laminar region (LR), which is clearly seen in the transition zone between both regions where it can be seen how the glial tubes are perfectly matched with the cribrosa pores [29, 30, 41].

2.2.3. Limiting membranes

In the prelaminar region, we find two other glial limiting membranes: the Kuhnt intermediary tissue, which separates the optic nerve from the retina, and it continues subsequently with the border tissue of Jacoby, which isolates the optic nerve from the surrounding choroidal tissue (**Figures 2A**, **3A** and **5A1**) [29, 41, 57, 59, 60].

Both limiting membranes are formed by thick cell body astrocytes that are arranged in densely packed 4–5 layers forming a separation barrier between the optic nerve, the retina and the choroid [29]. The barrier function is supported by the existence of tight junctions between the astrocytes of the Kuhnt intermediary tissue and the retinal pigment epithelium cells as well as the presence of desmosomes between the astrocytes and the outer limiting membrane [60]. This barrier function could explain the large number of myelin fragments and dense bodies, which are phagocytosed and degraded by the astrocytes that form these glial limiting membranes [29, 59].

Another function fundamentally attributed to the Kuhnt and Jacoby tissues is that they act as bearings that cushion the frictions that take place in the small displacements of the optic nerve during the movements of the eyeball. In this way, the suffering of the nerve fibres, which enter the nerve in the peripheral areas, is avoided. This can be corroborated by the parallel disposition of the astroglial processes, which are connected to each other by numerous desmosome and tight junctions. Furthermore, the large number of intermediate filaments existing in these astroglial processes would provide them a certain rigidity and tensile force [29, 30, 52, 55, 57, 60].

2.2.4. Microglia

In the PR, as in the rest of the ON, in addition to the astrocytes, we find microglial cells. Microglia is a subtype of glia of the central nervous system that is activated in response to neuronal damage [61, 62]. In the normal tissue, these cells are quiescent and have a branched shape with a small nucleus and a cell body with several processes (**Figure 4C**).

At the ONH, quiescent microglial cells (which are HLA-DR, CD45 and Iba-1+) are located on the walls of the large vessels, surrounding the capillaries in the glial columns of the PR and the cribriform pores of the LR. In the case of moderate or severe damage in the ONH, the microglia are activated [63–65], forming accumulations of amoeboid microglia in the lamina cribrosa and surrounding blood vessels [66, 67].

2.3. The laminar region

The lamina cribrosa (LC) forms a band of dense, compact connective tissue across the scleral foramen. Its sieve-like arrangement (the lamina cribrosa) transmits the axon bundles of the nerve and central retinal vessels through a series of round or oval apertures (pores) embraced by strong trabeculae [68]. In normal eyes, the number of pores that form the LC is among 550–650. Histologically, it has been estimated that the diameter of the pores varies between 10 and 100 μm and that it decreases towards the posterior part of the LC (**Figure 6A**) [69, 70]. The bulk of the LC is made up of a series of dense connective sheets (**Figures 3E1** and **E2**). The LC blend peripherally with the sclera and alternate with a series of glial sheets in a lamellar fashion. LC plates are composed of elastin; collagen types I, III, IV and VI; laminin; and heparan sulphate proteoglycan [52, 73–75]. The collagens and the elastic fibres act as shock absorbers of the tension that supports this area of the optic nerve. Proteoglycans play an important role in the biomechanical properties of tissues, in such a way that, by occupying an extensive volume in relation to their molecular weights, they can be compressed before a load and expanded when it disappears. As in the optic nerve, there is a gradient of hydrostatic pressure from the disc to the retrolaminar region [76]; the properties of these molecules are important to soften the pressure gradient [66].

Using trypsin digestion and scanning electron microscopy, it is possible to appreciate the structure of the LC plates. There are regional variations in the form of the LC plates. Therefore, the superior and inferior quadrants of the laminar sheets are thinner and sparser, resulting in the formation of larger pores than in the nasal and temporal quadrants (**Figures 6B** and **C**) [21, 69].
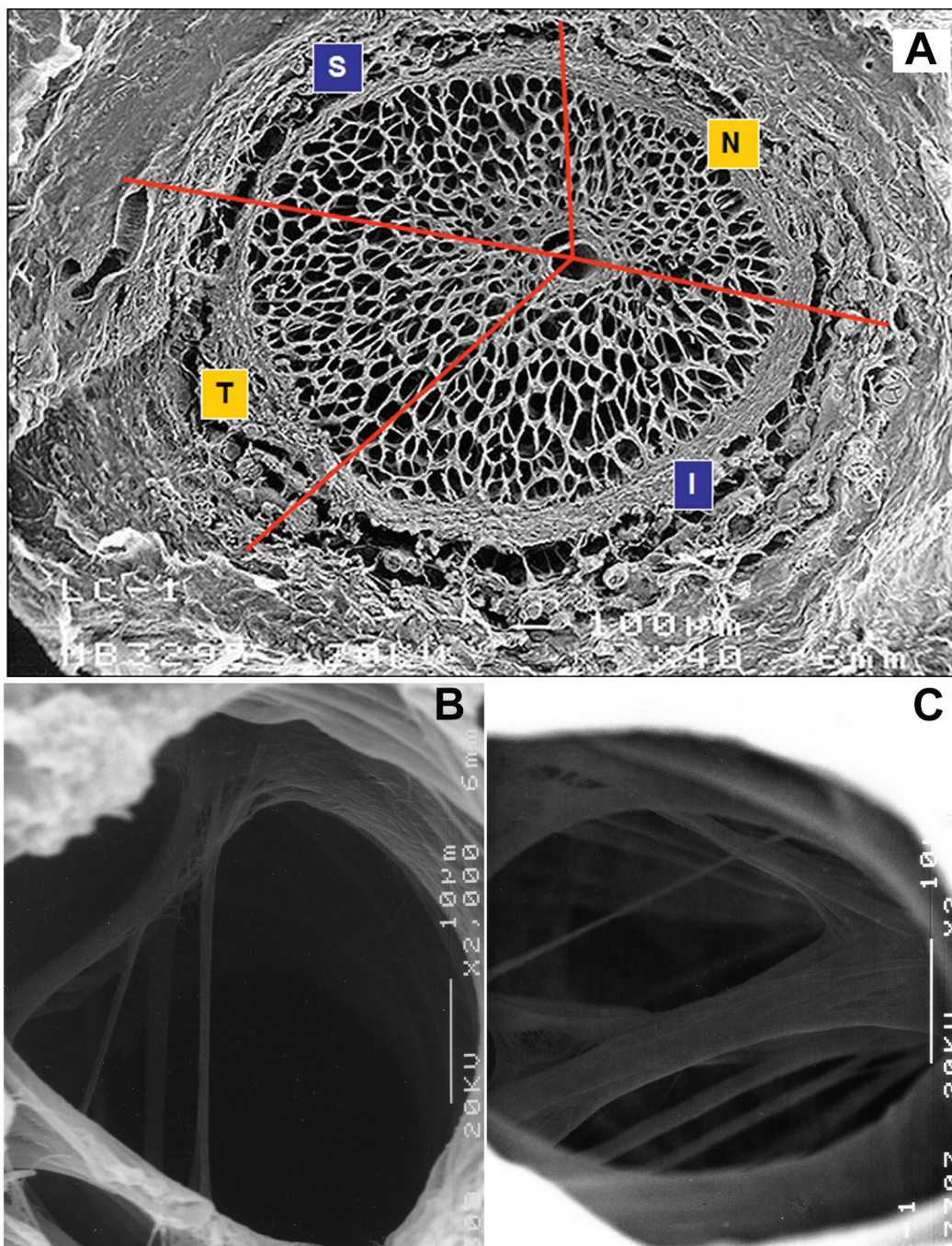
Figure 6. (A) Laminar region of the optic nerve head: Superior (S), nasal (N), inferior (I) and temporal (T) sectors. (B, C) detail of the cribriform pores: (B) nasal cribriform pore and (C) inferotemporal cribriform pore. (A–C) scanning electron microscopy with nervous tissue digestion by trypsin. (A: modified with permission from Ramírez et al. [181]).

There are two cellular types coating the LC plates: the LC cells and astrocytes (**Figure 3E2**). LC cells have been described as large, flat, broad and polygonal GFAP (−) alpha-smooth muscle actin (alpha-SMA)+ cells that possess multiple cell processes [71]. However, they take on a more oval shape in situ [72]. Although LC cells reside within the LC, astrocytes GFAP (+) are located in the plate openings alongside axon bundles as they transverse multiple plates [66, 71]. Ultrastructural evaluations show that LC cells are elongated with abundant cytoplasmic actin microfilaments and organelles, such as an active rough endoplasmic reticulum, a well-developed Golgi apparatus and a dense band of heterochromatin along the nuclear

membrane [77]. LC cells produce an increased expression of extracellular matrix (ECM) proteins if exposed to mechanical stimulation [78]. LC cells are now recognized as a major site of RGC damage in primary open-angle glaucoma. Cells within the LC have profound effects on the ECM environment and RGC survival. Autocrine or paracrine signaling of growth factors between cells of the LC may play a role in maintaining a homeostatic mechanism within the human LC [79].

Ganglion cell axons go through the pores of the LC. Most of the nerve fibres that pass through the lamina cribrosa take a direct course. However, between 8 and 12% of the fibres can be diverted to pass through the cribriform pores in the central and peripheral areas of the disc. Consequently, these axons could be more vulnerable to alterations of the LC [76].

It has been proven that there are significant correlations between the area, convexity and aspect ratio of a pore and the level of biomechanical insult to the neural tissues within the pore. The relationship between pore shape and neural tissue insult was observed for undeformed configurations. When deformed by intraocular pressure (IOP)-induced hoop stress, the pores became larger and more convex possibly reducing the risk for further insult [80].

It has been observed that damage to the neuroretinal rim in moderate glaucoma occurred mainly in the inferotemporal [81] and superotemporal regions [82], while the remaining portions of the neuroretinal ring in advanced glaucoma were found in the nasal region [82]. Quigley and Addicks [83] performed a histological evaluation of optic nerve axons at the LC and found that axon loss occurred in all regions but was greater in the superior and inferior regions of the LC. Furthermore, the pattern of axon loss corresponded to regional differences in the structure of the LC, which contained larger pores and thinner beams in the superior and inferior regions [22].

2.3.1. Glioarchitecture of the laminar region

With respect to the glioarchitecture of this region, there is a marked decrease in glial tissue, which only covers the internal face of LC plates (**Figures 3E1** and **E2**). The astrocytes have a thick cell body similar to those of the posterior PR but form a single layer that covers the inner wall of the LC pores (**Figures 3E1** and **E2**). The function of these cells is to provide functional support to axons and synthesize macromolecules of the extracellular matrix, which is also responsible for supporting the shearing and stretching forces generated by the displacement of the LC by the action of IOP [29, 30, 41, 84].

The core of the cribriform plates is separated from the astrocytes by a continuous and well-defined layer of type IV collagen, laminin and heparan sulphate proteoglycan (**Figures 3E1** and **E2**). These macromolecules form part of the basement membrane of astrocytes and contribute to form a network of filamentous material. This basement membrane fulfils a structural function by providing a flexible substrate for cell attachment. In addition, laminin plays an important role in the regulation of cell differentiation and proliferation of neural tissues [66, 76].

Cells are anchored to the basement membrane by membrane glycoproteins with adherent properties, having identified in the optic nerve by one of the main types of adhesion molecules, integrins [66].

Regarding their embryonic origin, the glial elements of the ONH are derived from ectodermal cells, but the mesenchymal cells of neural crest account for the development of the LC tissue and cells [77].

It is possible that LC cells are astrocyte precursors or develop into astrocytes because there is a large GFAP subpopulation of astrocytes existing in the brain [85, 86]. Thus, LC cells may be a subset of GFAP astrocytes but are different from the normal ONH astrocytes because of their different morphologies and immunostaining properties [72].

2.3.2. Vascularization of the laminar region

The LC is supplied by centripetal branches arising directly from the short posterior ciliary arteries or from the intrascleral circle of Zinn and Haller (**Figures 7A** and **8A**).

The posterior ciliary arteries (PCAs) originate from the ophthalmic artery and enter the ocular globe laterally, medially or superiorly to the optic nerve, which is why they are denominated lateral, medial or superior PCAs. The number of these vessels shows a marked interindividual variation (between one and five) [87] although the most frequent situation is the existence of two to three PCAs (**Figure 7A**) [88, 89].

In the case that there are only two PCAs (medial and lateral), these vessels irrigate the nasal and temporal portion of the choroid, respectively, finding a watershed zone that is the border between the territories of distribution of adjacent end arteries. Since the PCA circulation is the main source of blood supply to the optic nerve head, the location of the watershed zone between the PCAs is crucial in ischemic disorders of the ONH. This watershed usually runs vertically somewhere in the area between the fovea and the peripapillary nasal choroid (**Figure 7B**) [90–92]. On the other hand, if there are three or more PCAs, the watershed is usually Y-shaped, and it is located in a part of the optic disc. However, there may be different combinations of shapes in the watershed zones when there are more than two PCAs, depending on whether the area supplied by each PCA is a quadrant or only one sector. Thus, when the entire optic disc lies in the centre of a watershed zone, that disc is particularly vulnerable to ischemia [88, 89, 91, 93].

The ACPs are subdivided into several branches before perforating the sclera, which surrounds the optic disc. They are two long posterior ciliary arteries (LPCAs) and 15–20 short posterior ciliary arteries (SPCA) (**Figure 7A**) [94–96]. According to their scleral penetration, the SPCAs can be subdivided into para-optic SPCAs (closer to the optic disc) and distal SPCAs (**Figure 7A**) [97, 98].

In histological sections, SPCAs and LPCAs are characterized because they have the typical structure of small arteries with an endothelium and internal elastic lamina in the tunica intima, two smooth muscular layers in the tunica media and an adventitia constituted by circularly oriented collagen. The arterioles derived from these arteries present an endothelium covered with a basement membrane, a discontinuous muscular layer and a continuous collagen adventitia [9, 99–101].

Overall, two para-optic SPCAs penetrate and surround the optic disc constituting the Zinn-Haller arterial circle, which provides blood flow to the circumpapillary choroid and the prelaminar and
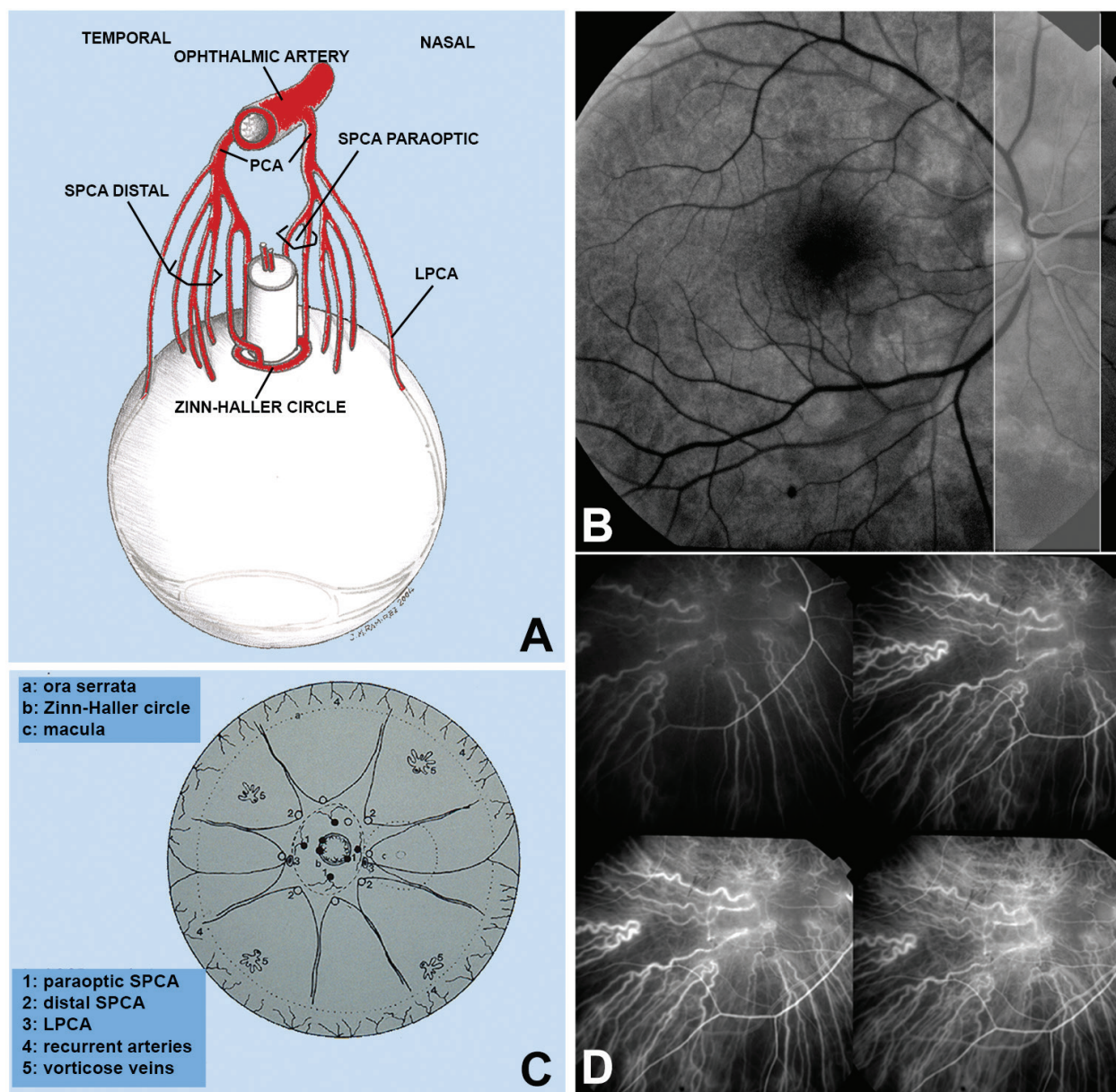
Figure 7. Ciliary system vascularization. (A) Three-dimensional scheme of the ciliary artery entrance in the eyeball. (B) Fluorescein angiography showing the watershed between the territories of the PCA (space between lines). (C) Scheme of the distribution of the branches of the PSCA in the human choroid. (D) Indocyanine green angiography of the sectoral division of the PSCAs that form triangular areas and the watershed zones between these branches [posterior ciliary arteries (PCA), short posterior ciliary arteries (SPCA), long posterior ciliary arteries (LPCA)].

laminar regions of the ONH, through capillaries originating directly from the Zinn-Haller circle (**Figures 5B2**, **7A** and **8A**). The rest of the SPCAs, both para-optic and distal, once in the choroidal vascular layer, divide sectorially forming triangular areas towards the four regions of the eyeball. These arterial ramifications (which generate the choroidal arteries) first are dichotomous, forming acute angles. The posterior ramifications can do so from acute angles to angles of 180°, carrying during its travel an undulating trajectory (**Figures 7C** and **D**) [94–96, 102].
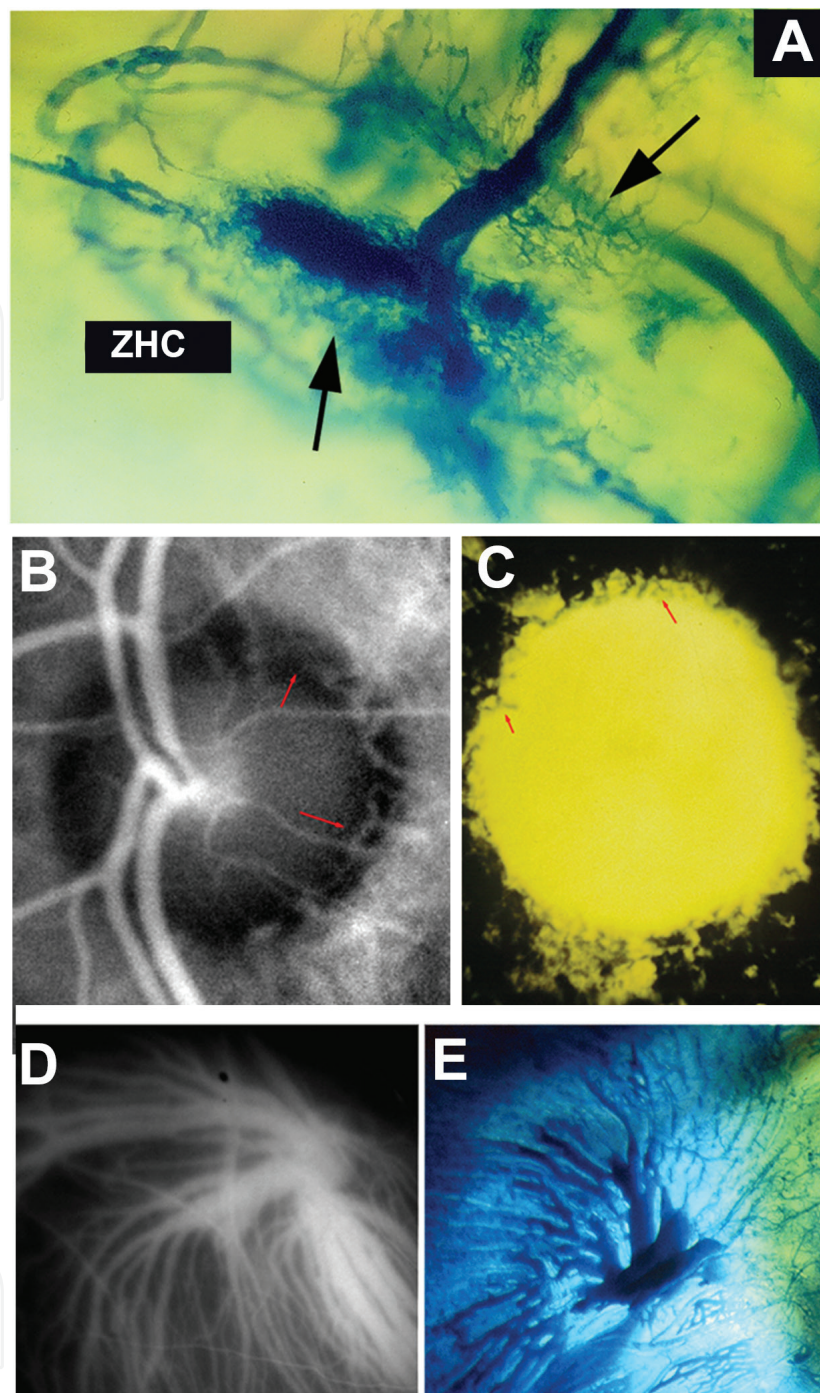
Figure 8. Ciliary system vascularization. (A) Zinn-Haller arterial circle (ZHC) (arrows) dependent on two short posterior ciliary arteries. (B, C) vascular branches of choroidal peripapillary precoriocapilar. Centripetal vessels (arrows). (D, E) Vorticose veins. (A, C, E) Diaphanization technique and vascular filling with polymers. (B) Fluorescein angiography. (D) Angiography with indocyanine green.

The macular region is irrigated by distal branches of the SPCAs, without observing, contrary to what was postulated by some authors (90–92) in any specific vessel for this region [96, 103–106]. The macular region is irrigated by a dense network of distal branches of SPCAs

[94]. Furthermore, this region corresponds to the area of the choroids, which presents a higher blood perfusion pressure and higher blood flow [107, 108].

The peripapillary region is mainly irrigated by para-optic branches of SPCAs and some branches from the Zinn-Haller arterial circle. This circle emits branches not only for prechoriocapillary peripapillary choroid but also for the PR and LR of the ONH (**Figure 8B** and **C**) [48, 96, 108–110].

Posterior ciliary arteries are end arteries. However, they are not completely so in the functional sense, because choroidal vascular occlusions frequently recover over a matter of days [90, 106, 111, 112]. There are watershed zones between the various PCAs (**Figure 7B** and **D**). The significance of the watershed zone is that in the event of a fall in the perfusion pressure in the vascular bed of one or more of the end arteries, the watershed zone, being an area of comparatively poor vascularity, is most vulnerable to ischemia [90, 111]. The existence of these watershed zones has been demonstrated between PCAs [90], SPCAs [106], SPCAs and LPCAs [113], anterior ciliary arteries and PCAs [112, 114], lobule of choriocapillaris [112, 115, 116] and the vorticose veins [112]. Moreover, its location on the macular region and the ONH could imply greater vulnerability of these areas to chronic ischemia [91].

The arterial and venous systems of the choroid are not parallel as they are in most systems of the body. Most of the vessels of the outermost choroid are mainly veins with the exception of those close to the optic disc and those located under the macula [117].

The veins collect blood from the anterior uvea, from the equator and from the posterior pole, to drain the entire choroid via vorticose veins. The choroidal venules and veins are larger than the arteries and maintain a rectilinear path, joining at many acute angles before ending in the vorticose veins [9, 99, 117].

Normally, there are four vorticose veins, two nasal (superior and inferior) and two temporal (superior and inferior) [118], although this number can vary between three and six. These veins are located equatorially (one for each quadrant) and form a bottle shape receptacle before its scleral perforation, which is accordingly constituted by the meeting of two to four ampulliform dilatations (**Figure 8D** and **E**) [97, 119]. Histologically, the veins present an endothelium (with its basement membrane), an irregular muscular layer and a fine collagen adventitia. Venules are broadly similar but have no muscle layer [99].

Classically, it has been described that each vorticose vein and its tributaries drained a quadrant of the choroid with little or no overlap between the other adjacent drainage quadrants. A boundary or edge (watershed) exists between these territories [120]. These limiting zones are arranged in the form of a cross, which crosses near the posterior pole, with the horizontal arm passing through the optic disc and the macula and the vertical arm between the optic disc and the macula [120]. Therefore, the temporal quadrant on the horizontal plane would be drained by the superior temporal vorticose vein, whereas the inferior temporal quadrant would be drained by the inferior temporal vorticose vein. According to this interpretation, these watershed areas would be regions that could be more affected by venous occlusions.

However, this interpretation is probably uncertain since more recent studies have shown that after the injection of coloured polymers into a vorticose vein, it was followed by an immediate exit of the dye by the other vorticose veins, suggesting the existence of anastomosis in the drainage system [121].

Therefore, it is currently accepted that the tributary branches of the vorticose veins are very anastomosing at all levels of their branch, and there may be shunts between the watersheds of the different tributary territories.

In addition, the studies performed with fluorescein angiography indicate that experimental occlusion in monkeys in vorticose veins originate a deficit in drainage as indicated by the persistence of fluorescence in the affected quadrant. Nevertheless, the realization of the angiography a few hours later shows that there is little or no deficit in the affected area. Therefore, the restoration of the normal flow pattern in the affected area implies the existence of alternative drainage routes, which could be due to venular anastomoses.

It should also be taken into account that the macular area and the area around the optic nerve represent the areas which are most distal to the choroidal venous drainage of the vorticose veins. As a result, these are areas where the choroidal venous pressure is highest, and therefore, they are the areas which are especially sensitive to any obstruction of the venular drainage [122, 123].

Recently, it has been postulated that a paravascular transport system, which is present in the eye is analogous to the recently discovered glymphatic system in the brain. It is a functional waste clearance pathway that promotes elimination of interstitial solutes, including β-amyloid, from the brain along the paravascular channels [124]. The glymphatic system was first described by Iliff et al. (2012) [125] as a brain-wide network of paravascular channels, along which a large proportion of subarachnoid cerebrospinal fluid (CSF) recirculated through the brain parenchyma, facilitating the clearance of interstitial solutes, including β-amyloid, from the brain. This anatomical pathway consists of a para-arterial CSF influx route, a para-venous interstitial fluid clearance route and a transparenchimal pathway, which are dependent upon astroglial water transport via the astrocytic aquaporin-4 water channel [126]. Iliff et al., 2013 [127], proposed that a similar glymphatic system or, at least, a paravascular system be present in the retina. Wostyng et al. (2015) [128] suggested that the glymphatic system may also have potential clinical relevance for the understanding of the pathophysiology of glaucoma. The presence of this clearance system would support the hypothesis that glaucoma as well as Alzheimer disease and may occur when there is an imbalance between the production and clearance of neurotoxins [129]. In addition, Mathieu et al. (2017) [130] provides the first evidence that CSF flows into the optic nerve through paravascular spaces that surround small perforating pial vessels as they enter into the optic nerve. This glymphatic pathway is comprised of centripetal spaces bonded by blood vessel walls on one side and aquaporin-4+ astrocytic endfeet on the other. A dysfunction in the glymphatic system in glaucoma patients would support the hypothesis that CSF circulatory alteration may play a contributory role in glaucomatous damage.

2.3.3. Biomechanics of the laminar region

LC is believed to be the site where the main damage to the axons of the CGRs in glaucoma can occur. It is an interesting region from the biomechanical point of view, since within this site, there is a discontinuity in the corneal-scleral covering that constitutes a weak point in the mechanical load systems, and therefore, this is where the stress can be concentrated [131].

An increase in IOP can act mechanically in the tissues of the eye, producing deformations, tension and stress, which will be larger or smaller depending on the geometry and the material properties of each eye. When the levels of stress and tension exceed the physiological tolerance of the tissue cells, they can induce remodelling of the connective tissue (increase the production or eliminate collagen and elastin), in an attempt to return to a mechanical environment homeostasis [132]. This increase in the connective tissue could seriously alter the blood flow by compression of the vessels derived from the Zinn-Haller circle and therefore affect nutrition in the laminar region. It must be taken into account that this could all occur with the IOP within the normal range in those eyes, which are particularly susceptible to IOP-related stress [133, 134]. It is believed that connective tissue disorders, related to IOP, can cause the anterior lamellae of the LC to give way or be destroyed, thereby transferring the load (weight) to adjacent lamellae in a cascade of damage that would help cause, together with the loss of axons, the glaucomatous excavation [135, 136].

The LC forms a barrier between two differentially pressurized compartments: the intraocular space with higher pressure (IOP) and the retrobulbar space with a lower pressure retrobulbar cerebrospinal fluid pressure (CSFP). A pressure gradient is formed cross the LC. The pressure difference between the two compartments is denominated the translaminar pressure difference (TLPD) and is defined as IOP-CSFP. At a given IOP, subjects with a lower CSFP have a larger TLPD, which can result in the posterior deformation of the LC [137, 138]. The ability of the LC to tolerate a given TLPD without being deformed may be associated with the material properties (compliance, stiffness or structural rigidity) and geometry (thickness, shape or curvature) of the LC and the peripapillary connective tissues [135, 139]. Based on the notion that the translaminar pressure dynamics may influence LC deformation and an optic nerve axoplasmic transport, it can be speculated that eyes with a larger TLPD or translaminar pressure gradient (TLPG) may have an increased susceptibility to glaucomatous damage. Posterior deformation of the anterior LC surface is considered one of the key manifestations of glaucomatous optic neuropathy [136].

A high translaminar pressure gradient can induce the blockade of the axonal flow within the optic nerve fibres at the level of the LC [140, 141]. The TLPG may be influenced by the properties of the other structures, such as low CSFP [142–144] and a thinner LC, both of which increase the TLPG [140, 145–147]. It has been reported that a thinner central corneal thickness (CCT) is a risk factor for the conversion of ocular hypertension to primary open-angle glaucoma [148, 149] because of a thin cornea inducing a falsely low IOP measurement and a thin cornea being associated with a more susceptible optic nerve complex. However, histologic studies have found that there is no significant correlation between CCT and LC thickness [150, 151].

The deformation, the mechanical stress and the consequent increase of the collagen in the LC cause the axons to suffer deformations and mechanical stress as it passes through the pores of the LC. This can produce a mitochondrial dysfunction, which leads to a lower production of energy, triggering a blockage of the axonal transport of molecules, among which there exist neurotrophic factors (such as BDNF) which originate in the brain. These neurotrophic factors are transported towards the soma of the CGRs. The decrease of these factors, which is important for the regulation of metabolism and cell survival, can lead to the progression of the death of CGRs by apoptosis. Therefore, the alteration of the axoplasmic flow would be one of the first events that induce CGR apoptosis in glaucoma.

As we have already mentioned, the mechanical stress generated by IOP produces the reactivation of the astrocytes, causing the remodelling of the ECM. The integrins would act as mechanosensors intercommunicating the astrocytes with the ECM. In this remodelling, there is an increase in type VI and type IV collagens (the latter being a constituent of the astrocyte basement membrane) which will modify the original structure of the cribriform pores. In addition, proteoglycans and glycosaminoglycans can also be modified and the elastic fibres can degenerate. All of this leads to the biomechanical alteration of the tissue described previously.

The ECM is also responsible for providing adhesion signals, thereby controlling the functions of cells and cell survival. Reactive astrocytes increase the activity of matrix metalloproteinases (MMPs), which are enzymes involved in ECM remodelling in such a way that they can degrade cell adhesion molecules to allow cell mobility. Therefore, changes in the specific components of the ECM (increased MMP-9, laminin loss, etc.) can interrupt cell–cell and ECM-cell interactions, which could cause, in the case of CGRs, cell death by apoptosis.

Tenascins represent key constituents of the ECM with a major impact on the central nervous system development. Several studies indicated that they play a crucial role in axonal growth and guidance, synaptogenesis and boundary formation. These functions are not only important during development but also for regeneration under several pathological conditions. Tenascin C represents a key modulator in the immune system and inflammatory processes [152]. It is not only involved in barrier formation, but it is also a constituent of the glial scar after injury. Furthermore, it might be implicated in reactivation of astrocytes which play a crucial role in glaucomatous optic nerve fibrosis [153].

2.4. The retrolaminar region

This zone extends from the end of the LC to the place where the central blood vessels (CRA and central retinal vein) enter the optic nerve (**Figures 2A** and **3A**).

The retrolaminar region (RLR) is a part of the intraorbital portion of the optic nerve and, as such, is surrounded by the meningeal sheaths: dura, arachnoid and pia mater. These leave two spaces called subdural (between the dura mater and the arachnoid) and subarachnoid (between the arachnoid and the pia mater) (**Figure 9A**).

This region is distinguished by the appearance of oligodendrocytes that myelinate the axons of this zone (**Figures 3F1, F2** and **9C**). The bundles of axons are arranged in a polygonal shape
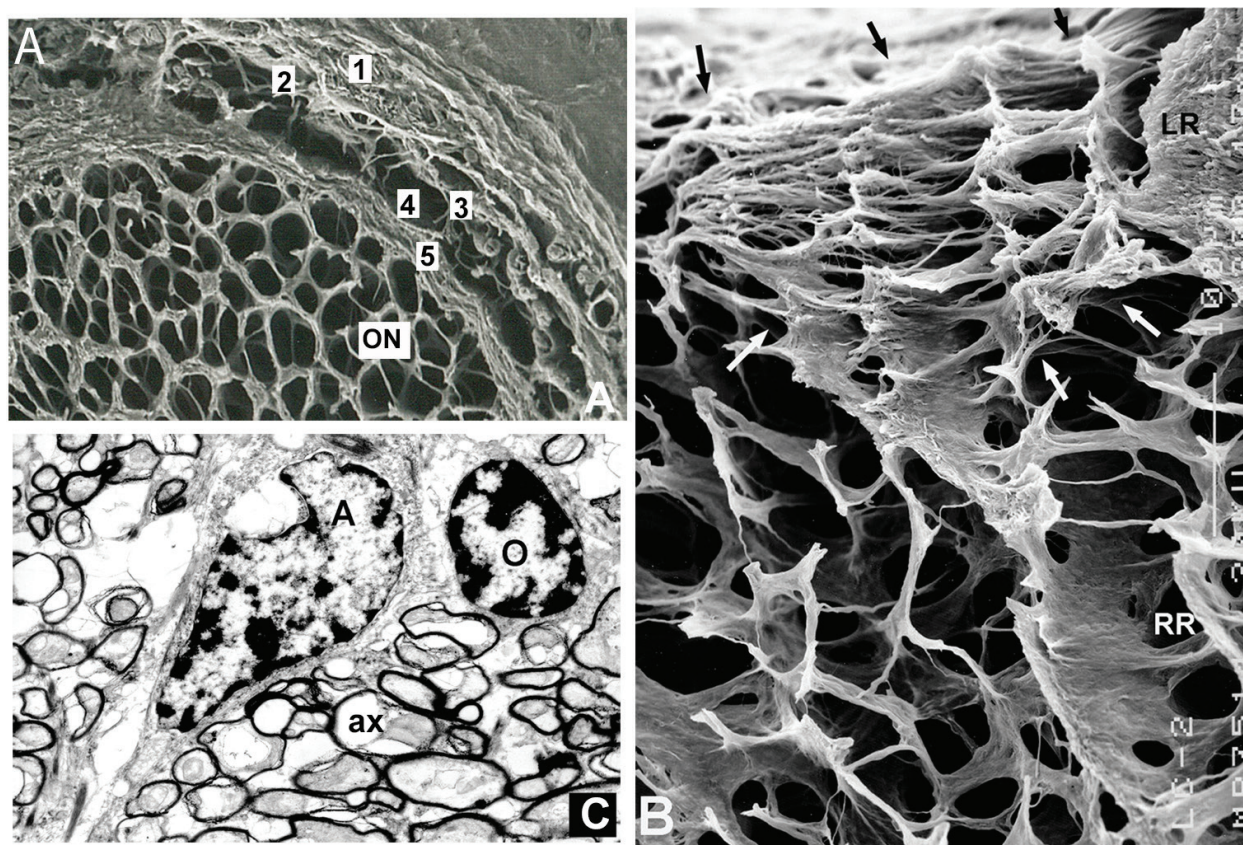
Figure 9. Retrolaminar region. (A) Meningeal sheaths surrounding the retrolaminar region of the optic nerve (ON). (1) dura mater, (2) subdural space, (3) arachnoid, (4) subarachnoid space, and (5) pia mater. (B) Connective septa. The arrows indicate the laminar region (LR). Retrolaminar region (RR). (C) Transmission electron microscopy showing the astrocytes (a), myelinated axons (ax) and oligodendrocytes (O). (A, B) scanning electron microscopy with nervous tissue digestion by trypsin. (C) Transmission electron microscopy.

and surrounded by connective tissue septa (**Figure 9B**). These septa are attached to the pia mater peripherally, to the lamina cribrosa in its anterior portion and to the connective tissue of the adventitia of the CRA in its central portion. These septa are also responsible for driving the vessels into the interior of the optic nerve [29].

Axon diameter along with myelin thickness [154], internode [155] and paranode gap [156] determines the functional properties of the nerves [157]. Axon diameter has been used to determine conduction velocity along various pathways. Thus, this indicates that there is a strong link between structure and function in the central nervous system. The characterization of ultrastructural properties of the axons has proven useful in exploring the pathology of neurological condition [155]. In the axons, the mitochondria are accumulated around the areas of highest energy demand, such as the nodes of Ranvier, in which the ATP is necessary to maintain the activity of the energetically demanding Na^+/K^+ ATPase ion pumps [158, 159]. Mitochondria change their morphology according to the energy status of the cell in processes referred to as fusion and fission [160].

2.4.1. Vascularization of the retrolaminar region

The vascularization of the optic nerve in this region varies in function of the central or peripheral location of the tissue. Thus, the axial or central zone is fundamentally nourished

by the vessels coming from the CRA, while the peripheral zone receives vessels from the CRA through its pial arteries or vessels derived from the ciliary system from Zinn-Haller circle and the peripapillary choroids. In the most posterior areas, the contribution from the branches of the ophthalmic artery and its collaterals is important (**Figure 10A**) [8, 41, 43, 161].

2.4.2. Macroglia and microglia of the retrolaminar region

There are three types of glial cells in the retrolaminar region:

- Astrocytes which contribute to the fasciculation of axons and their separation from blood vessels and connective tissue. In this region, the main fasciculation of the axons is carried out by the connective septa (**Figures 3F2**, **9B** and **C**)

- Microglia which are scarce cells, but they are, in a proportion, similar to those of the rest of the optic nerve (**Figure 4C**)

- The oligodendrocytes which are responsible for the formation of the demyelin sheaths of the axons (**Figures 3F2** and **9C**)
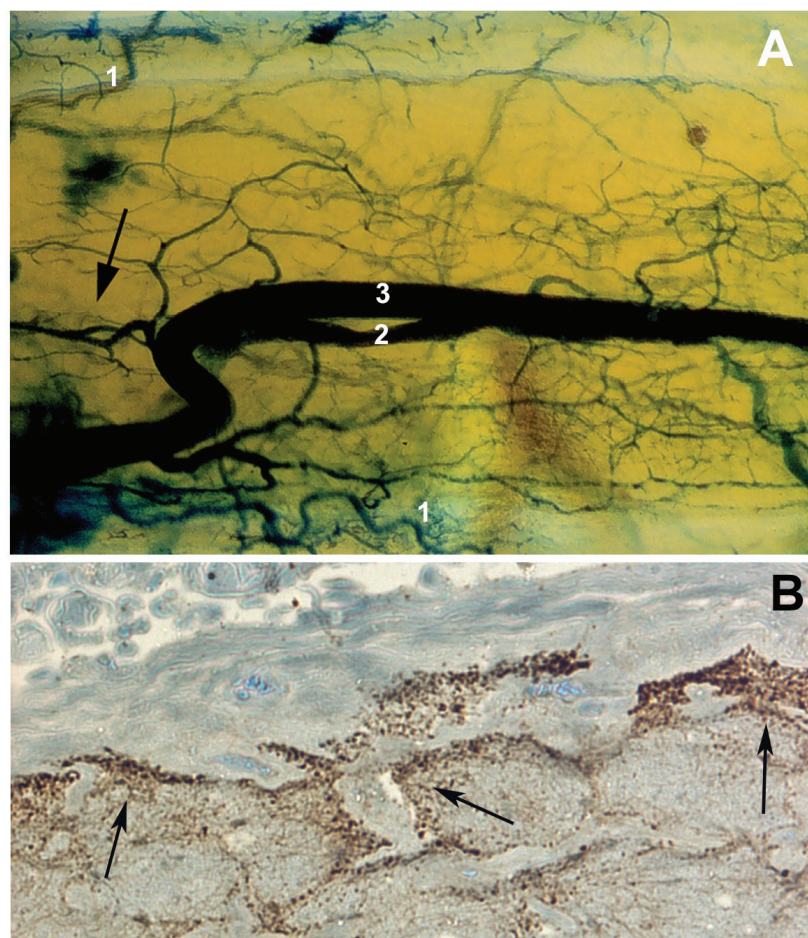

Figure 10. Retrolaminar region. (A) Vascularization: (1) pial vascularization, (2) central retinal artery, and (3) central retinal vein. (B) Peripheral glial mantle of Graefe (arrows). (A) Diaphanization technique and vascular filling with polymers. (B) Immunohistochemistry GFAP-Ünna-Tanzer.

The appearance of myelin in this area causes the thickness of the nerve to increase double in comparison to the level observed in the LC, going from 1.5 mm to 3 mm. Myelination of the nerve is necessary for the saltatory conduction of the nerve impulse. The absence of myelin can be lethal, and this has been demonstrated in animals that have a mutation in myelin proteins such as proteolipid protein (PPL) and myelin basic protein (PBM). In addition, the demyelination of axons causes neurological dysfunctions as those observed in multiple sclerosis [8].

In cell cultures, it has been shown that oligodendrocytes and astrocytes originate from a common precursor, the bipotential cells A2-B5+ [162–164]. These can generate to both a subpopulation of astrocytes called type 2 and oligodendrocytes, which is why they have been called progenitors of oligodendrocyte-type-2 astrocytes (O-2A) [164, 165].

The differentiation of progenitors O-2A into astrocyte type 2 requires environmental signals such as the interaction of a ciliary neurotrophic factor (CNTF) [166] with components of the ECM [70]. The absence of these signals generates oligodendrocytes [167, 168].

The maturation of oligodendrocyte precursors occurs in a series of stages recognized by the expression of different surface antigens, by morphological and motility characteristics and by the response to specific growth factors [169]. The precursors of the immature A2B5+ oligodendrocytes are very mobile. They have a characteristic bipolar morphology and express surface antigens which include the glycoprotein NG2 and the ganglioside GD364. As the precursor matures, it becomes less mobile and more processes appear. Although it retains its positivity for A2B5, it begins to express additional antigens, which include an antigen denominated POA [6], which is recognized by the antibody monoclonal O4 [170] (O4+ cells). At a later stage of maturation, high levels of galactocerebroside, which is the main glycolipid of myelin, are expressed [164].

The elaboration of myelin sheaths is associated with the expression of specific myelin components such as the basic myelin protein (MBP) and the proteolipid protein (PPL) [10, 171].

The proliferation of the oligodendrocyte precursor is induced by different mitogens at different stages of development. The precursor of the immature oligodendrocyte A2B5+ proliferates mainly in response to a platelet-derived growth factor (PDGF) and to a lesser extent to the growth factor of type II fibroblasts (bFGF) [172]. The precursors of the most mature oligodendrocytes O4 (+) do not respond to PDGF but retain their proliferative response to bFGF.

Experimental studies with lipophilic dyes have shown that the origin of the oligodendrocyte precursors of the optic nerve is found in the floor of the III ventricle, producing a migration from this zone to the chiasm and subsequently to the optic nerve [173]. The production of tenascin C by astrocytes regulates the migration of oligodendrocyte precursors at the level of the LC [170]. It has been suggested that glial precursors use similar molecular cues to those that guide axons during central nervous system development. These signals have been characterized as netrin-1 for oligodendrocytes and semaphorin 3a for astroglial cells [174].

The oligodendrocytes will be responsible for the formation of the myelin sheath, while the type-2 astrocytes would be in charge of the maintenance of the nodes of Ranvier, controlling

the perinodal ion concentrations and providing nutrients to the axon [8]. The nodes of Ranvier are the areas of the axon where the myelin is interrupted. Its importance lies in the fact that the propagation of action potentials takes place by jumping from node to node, which leads to greater efficiency in nerve conduction. The astrocytes send perinodal processes that surround the unmyelinated axonal plasma membrane. This association suggests that it may play an important role in the physiology of the node, in such a way that specific conditions can be created to generate action potentials [175]. The astrocytes, therefore, could synthesize and renew ion channels of the nodal membrane. In addition, the sodium channels of the perinodal astrocytes could be involved in the ionic homeostasis of the perinodal space, in which the ion buffers the perinodal space dependent on the electrical activity of the node [8].

There is another cellular type in relation to nodes of Ranvier called NG2-glia. These cells express the NG2 chondroitin sulphate proteoglycan. NG2-glia share many morphological features with astrocytes but do not appear to express the conventional mature astrocyte markers (GFAP, vimentin, S-100, glutamine synthetase) and do not contain intermediate glial filaments. However, NG2-glia, in the CNS, have not only been considered to be adult oligodendrocyte progenitor cells (OPC) based on their antigenic phenotype but also to be equivalent to O-2A cells. The possible role of these cells could be to monitor and respond rapidly to changes in axonal activity, resulting in stereotypic injury response and possibly in the regeneration of remyelinating oligodendrocytes [176]. Nevertheless, other authors have found NG-2 expression in astrocytes and confirm the non-selective nature of NG-2 expression since some populations of astrocytes express the antigen [177].

In the retrolaminar region, as in the other parts of the nerve, there exists a glial tissue formed by thick bodied astrocytes, which separate the pia mater from the optic nerve axons. It is denominated the peripheral glial mantle of Graefe (**Figure 10B**). The characteristics of this glial mantle are similar to those of the other limiting glial membranes previously described in the optic nerve [29, 171, 30]. Furthermore, in these subpial astrocytes, the existence of invaginations in the plasma membranes called caveolar vesicles have been described, as well as contractile microfilaments. The function of both is to initiate the contraction of the peripheral glial mantle of Graefe in response to the stresses that may occur in the meningeal sheaths of the optic nerve [178].

2.5. Blood-central nervous system barriers

The central nervous system is a very sensitive system in the human body. Thus, the presence of specialized structures to maintain a stable ionic environment that allows correct neuronal activities and isolates the neurons from the cerebrospinal fluid and blood is necessary [179]. Based on this, capillaries of the central nervous system have tight cell junctions between endothelial cells, low numbers of pinocytic vesicles, and specific transporters (the blood-brain barrier), so that they can control fluid and molecular movement and provide a barrier effect against the leakage of materials from the capillaries [181]. In the ocular central nervous system, there are two types of blood-tissue barriers: the blood-retinal barrier (BRB) and the blood-optic nerve barrier (BONB) [181].

Molecules can be transported through barriers, but it is a highly regulated process. The molecules are transported in two ways. Firstly, the paracellular pathway is regulated by the dynamic opening and closing of the inter-endothelial junctions. Secondly, the transcellular pathway involves the formation of specialized transport vesicles (the caveolae) and the transport mediated by receptors [182, 183].

The paracellular pathway restricts the passage of solutes of more than three nm and is the preferred route for the passage of water and small water-soluble compounds [184]. The junctions between the endothelial cells are formed by tight junctions, adherent junctions and gap junctions. The tight junctions are interspersed with adherent junctions, which are formed before tight junctions favouring their formation. Gap junctions can facilitate the assembly of tight junctions and adherent junctions [182]. The main proteins of the tight junctions are the occludins and the claudins that form a barrier and regulate the permeability [185, 186]. Moreover, the ZO-1 is an adapter protein that connects to the cytoskeleton, which can participate in the contraction of the cells and therefore regulate the dynamic opening of tight junctions [187].

The transcellular pathway (or transcytosis) is the preferred route for the active transport of macromolecules. It is carried out through caveolae and transport mechanisms mediated by receptors. In hemato-nervous barriers, transcytosis is different from the endothelium, which does not form a barrier, and therefore, they have a lower number of caveolae (mainly on the side of the lumen) and express less caveolin-1, albumin receptors, and other molecules.

Other cells that regulate BRB and BONB are the pericytes, which are part of the neurovascular unit. In the retina, the relationship between endothelial cells and pericytes is 1:1 suggesting an important role of pericytes in the BRB. Pericytes are arranged around capillaries wrapped in the basal membrane and communicate with endothelial cells, macroglia (astrocytes, glia Müller), microglia and neurons. Although the basal membrane of the endothelial cells, both cells at some points separate, the pericytes make direct contact. The direct pericyte-endothelial contact is established via junctional complexes located to peg-socket contacts at sites were the basement membrane is absent [188]. The interactions between both cell types are important for the maturation, remodelling and maintenance of the vascular system through the autocrine and paracrine regulation by growth factors, as well as for basal membrane modulation [189]. During the development, the release of PDGF-B by the endothelial cells attracts the pericytes, forming tight junctions immediately after their recruitment. In addition, pericytes are able to attract glial cells [190].

The concept of the so-called neurovascular unit (NVU) is wider because the neurons and microglial cells are part of the cells involved in the blood barrier regulation. This neurovascular unit is composed of [186]:

1. The tight junctions between the endothelial cells, which restrict paracellular diffusion and effectively 'seal' the vessels

2. The continuous basal membrane that lines the endothelial cells

3. The pericytes that are embedded within this matrix, located between the endothelial cells and the astroglial endothelial feet

4. The processes of astrocytes, which communicate with the neurons and local synapses, as well as [183] cover the vessels, known as 'vascular feet'

5. Resident microglia, which can monitor its microenvironment with their processes and respond quickly to insults at or near the NVU

6. The retinal neurons

2.5.1. Blood-retinal barrier (BRB)

The internal BRB is established by the tight junctions of the endothelial cells of the retinal capillaries. These cells, which form a continuous layer, are arranged on a basement membrane, which is covered by astrocytes and the Müller cell processes, sealing the retinal capillaries. In addition, in many areas the basement membrane unfolds around pericytes. The latter do not form a continuous layer and therefore do not contribute physically to the diffusion barrier. Pericytes, astrocytes and Müller's glia can influence the activity of endothelial cells of the retina and therefore barrier properties, sending them regulatory signals (such as cytokines), which indicate changes in the microenvironment of neuronal circuits [191].

2.5.2. Blood-optic nerve barrier (BONB)

The capillaries of the optic nerve have barrier properties due to the presence of tight inter-endothelial cell junctions. In addition, in the optic nerve, the pial vessels and the Kuhnt intermediary tissue (located between the outer retinal layers and the ONH prelaminar region), which are also composed of astrocytes, also form a well-established blood-tissue barrier [181]. In the tissue of Kuhnt, the barrier consists of the tight junctions between the astrocytes of this tissue and the epithelium pigment of the retina, in addition to the desmosomes between the astrocytes and the outer limiting membrane [192]. However, the border tissue of Jacoby, which is located between the choroids and the ONH, and is composed of astrocytes, has defects in the barrier, which allows the filtration of the materials through them [192, 193]. Because the endothelial cells of the choriocapillaris have fenestrations, much of the material is freely filtered through the Jacoby border tissue to enter the prelaminar region of the optic nerve [179].

Another site where the BONB is not absolutely perfect is the prelaminar region. When a tracer was used to analyse the permeability of this region, it was observed that the prelaminar region showed a diffused distribution of the tracer in its extracellular spaces. The tracer was most concentrated in the posterior part of the prelaminar region and aggregated densely in the glial columns and around the capillaries in the ONH. The border of tissue of Jacoby was densely infiltrated. The diffusion of the tracer was less extensive in the lamina cribrosa and in the retrolaminar optic nerve region than in the prelaminar region [192, 194]. The microvessels in the prelaminar region of the ONH lacked classical barriers in the blood tissue and showed a non-specific permeability, possibly mediated by vesicular transport [195]. The absence of BONB in the prelaminar region would nullify the advantages attributed to barriers in the optic nerve blood vessels and could play a role in the development of noninflammatory optic neuropathies [180]. In the CNS there is only one other site in which there is a no blood-brain barrier, the postrema area (a small area located in the lateral wall of the fourth ventricle) [180].

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Conflict of interest

The authors have no conflicts of interest to declare.

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