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Review Article

The Retina as a Bridge to the Brain: Shared Neurodegenerative Mechanisms and Therapeutic Perspectives

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Abstract

The eye is a highly specialized structure that allows humans to know, understand and recognize the world around them through vision. The retina represents a specialized anatomical and functional extension of the central nervous system. Increasing evidence suggests that multiple retinal disorders share common molecular and cellular pathways with neurodegenerative diseases of the brain. This review explores the concept of the retina as a biological bridge to the brain, emphasizing the structural, embryological and physiological continuity between these systems.

We analyze key mechanisms involved in both retinal and brain degeneration, including glutamate dysregulation and excitotoxicity, optic neuritis and demyelination, vascular dysfunction and glymphatic system impairment. These mechanisms contribute to neuronal damage through mitochondrial dysfunction, oxidative stress, disruption of blood-tissue barriers and persistent neuroinflammation. Retinal ganglion cells, due to their high metabolic demand and mitochondrial vulnerability, emerge as particularly susceptible targets of these pathological processes.

This review also highlights parallels between retinal and neurodegenerative disorders, including neuronal death driven by glutamate excitotoxiciy, optic neuritis and multiple sclerosis and the mechanistic links between glaucoma and Alzheimer's disease.

Finally, emerging therapeutic strategies are discussed, with particular focus on stem cell and exosome therapies. Through immunomodulatory, neuromodulatory and bioenergetic mechanisms these approaches may offer multi-target strategies capable of addressing complex neurodegenerative disorders affecting both the retina and the brain.

Keywords: Glial Cells; Glutamate Excitotoxicity; Glymphatic System; Retina; Stem Cells

Abbreviations

CNS: Central Nervous System; ON: Optic Neuritis; RGCs: Retinal Ganglion Cells; BRB: Blood-Retinal Barrier; CSF: Cerebrospinal Fluid; IOP: Intraocular Pressure; ROS: Reactive Oxygen Species; BBB: Blood-Brain Barrier; MS: Multiple Sclerosis; MOGAD: Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease; NMOSD: Neuromyelitis Optica Spectrum Disorders; AQP4: Aquaporin-4; Aβ: Amyloid Beta

Introduction

The eye is a highly specialized sensory structure that allows humans to know, understand and recognize the world around them through vision. Vision impairment is a problem that affects a large number of people around the world, both young and old and

represents a real public health issue. This results in a profound impact on patients, increasing the risk of falls, accidents, social isolation and depression [1]. In turn, this leads to a loss of autonomy in activities of daily living, preventing individuals from reading texts and performing their normal activities [2]. On the other hand, in older adults, visual impairment is associated with deficits in cognitive performance [3]. The economic burden related to productivity loss and long-term care is substantial, placing significant strain on the healthcare systems globally [4].

Vision is undoubtedly one of the most important human senses, yet we still have much to learn about its anatomy, physiology and pathology. The aim of this review is to present the eye as a direct bridge to the brain, with the retina being an essential part of the Central Nervous System (CNS) rather than an isolated component. Eye and brain should no longer be studied or treated in isolation;a combined ophthalmological and neurological approach is necessary [5]. To this end, we will provide an overview of the anatomy and embryology of the eye, focusing on the retina as a vital CNS component.

This review highlights the concept of the eye as both, a bridge and a window to the brain. There is increasing evidence suggesting that several mechanisms involved in retinal degeneration resemble those observed in central neurodegenerative disorders. We will focus on the following mechanisms: glutamate dysregulation and excitotoxicity, Optic Neuritis (ON) and demyelination and glymphatic system impairment. The convergence of these mechanisms challenges the traditional, compartmentalized view of ocular disease calling for a more comprehensive neuro-ophthalmological approach.

Finally, we provide an overview of emerging therapeutic approaches for retinal degenerative diseases. The ability to restore vision is one of the most profound interventions a physician can offer [6]. To this end, we will provide a collection of past experiences in the use of stem cell and exosome therapies for retinal and neurodegenerative diseases in recent years, highlighting their immunomodulatory and neuromodulatory properties to correct the various pathophysiological mechanisms involved in retinal damage.

By framing retinal pathology within a broader neurobiological context, we will present a paradigm in which retinal disorders are approached not solely as localized ocular conditions but also as manifestations of CNS-related neurodegenerative processes.

Anatomy and Embryology Overview

The wall of the eye consists of three concentric layers which, from the outside to the inside, are: the fibrous tunic, the vascular tunic and the nervous tunic. The outer layer consists of the cornea and sclera, the middle layer comprises the iris, ciliary body and choroid. Lastly, the inner layer is the retina, a complex structure of neurons that capture and process light [7].

The human retina is a complex mosaic made up of five major classes of neurons that process the light entering the eye. These neurons are: amacrine cells, bipolar cells, horizontal cells, photoreceptors and Ganglion Cells (RGCs) [8]. The latter are the first neurons in the visual pathway. Their axons reach the retinal nerve fiber layer where they converge at the optic nerve head. As this nerve passes through the lamina cribrosa, it is surrounded by the three meningeal layers and Cerebrospinal Fluid (CSF) fills the subarachnoid space, a feature characteristic of the CNS [9]. Unlike other cranial nerves, the optic nerve is a true extension of the CNS. Consequently, it is myelinated by oligodendrocytes rather than Schwann cells [10].

The process of ocular development begins with the formation of the optic vesicles. The walls of the diencephalon then bulge outwards, coming into close contact with the surface ectoderm where the lens placode is formed. Each optic vesicle contains retinal stem cells which give rise to all the neuroectoderm-derived cells of the eye [11]. The neural retina, which develops from an evagination of the diencephalon of the brain, is a neural ectodermal derivative and is, therefore, considered to be part of the CNS [12].

This anatomical and embryological overview highlights the structural continuity between the eye and the CNS, providing the foundation for a deeper analysis of retinal physiology and its direct connection to the brain.

The Retina: Beyond a Sensory Organ

Vision constitutes the dominant sense in many species, with 50% of the cerebral cortex in macaque monkeys and 20-30% in humans being devoted to visual processing [13]. The retina exhibits a level of structural and functional complexity that extends

far beyond traditional textbook descriptions. This is also true for other CNS structures such as the hippocampus or the cerebral cortex. Rather than being composed of a few main actors surrounded by secondary actors, it consists of many anatomically equipotent microcircuits [14]. As no other part of the CNS can be directly observed by a physician, the retina opens a window to the brain. Its intricate organization makes it a unique and accessible window to the brain [8]. These two structures share functional similarities, degenerative and regenerative processes and a unique mechanism of crosstalk with the immune system [15]. This unique convergence of accessibility and neurobiological complexity positions the retina not merely as a peripheral sensory organ, but as a highly specialized extension of the brain.

Retina Anatomy and Synaptic Transmission

The retina is the innermost layer of the nervous tissue in the eye. It receives light stimuli and marks the beginning of the visual pathway. Behind the retina is the optic nerve, a true tract of the CNS. As mentioned above, the retina has five main types of neurons: amacrine cells, bipolar cells, horizontal cells, photoreceptors and RGCs. On the other hand, there is a distinct population of cells that provide support and maintain homeostasis at the retinal level: glial cells. The retina contains different types of glial cells with different characteristics. Together, these cells are essential for the maintenance of the Blood-Retinal Barrier (BRB), which is the target of various pathologies at the retinal level, with severe consequences for vision. Müller cells are the most predominant glial cells, followed by astrocytes and microglia [16].

Müller cells are specialized radial glial cells that span the entire retina. They largely contribute to nutrient metabolism, regulation of retinal blood flow and modulation of neuron excitation, among others [17]. These cells play a key role in the regulation of the neurotransmitter glutamate, which is essential for nerve transmission in the retina. Müller cells have the ability to modulate neuronal excitability, producing a true neuronal-glial-neuronal feedback loop that is essential in regulating retinal excitability [18]. As we will see later, this balance is impaired in retinal diseases that involve glutamate excitotoxicity, leading to neuronal death, especially of RGCs.

The different retinal cells are distributed across the 10 layers of the retina, among which we highlight the following: retinal pigment epithelium, photoreceptor layer, inner nuclear layer, ganglion cell layer and nerve fiber layer. The retinal pigment epithelium is located between the retinal photoreceptors and the choroidal capillaries. It plays a key role in maintaining the function and structure of the retina, transporting nutrients, absorbing the light and protecting the retina from photooxidation [19].

The photoreceptor layer has the primary function of absorbing the light. The retina contains two major classes of photoreceptors: rods and cones, the latter comprising three subtypes. They are essential for the conversion of light energy into electrochemical signals that provide the brain with accurate information about the surrounding environment [20]. Photoreceptors convert light energy into changes in membrane potential that modulate tonic synaptic transmission to second order neurons [21]. Bipolar cells are the neurons responsible for connecting photoreceptors to RGCs and amacrine cells. In the inner plexiform layer, bipolar cells make synaptic contact with RGCs [8]. RGC axons form the optic nerve and the electrical signals carried by these axons establish the initial connection between the outside world and our internal perception of sight, which is then processed by the brain [22]. As we can see, the retina is a complex structure with a rich neural network supported by a large population of supporting cells that maintain the homeostasis and structure of this system. This intricate cellular architecture and tightly regulated synaptic organization awards the retina a level of neurobiological complexity comparable to other central nervous system structures. Disruption of these tightly controlled mechanisms underlies pathological processes that are similar to those observed in central neurodegenerative disorders.

Blood-Retinal Barrier and Ocular Glymphatic System

The BRB maintains homeostasis in the retina, preventing the entry of blood-borne proteins into the retina and maintaining ionic and metabolic gradients. Blood-tissue barriers are typical of neural structures such as the retina, nerves and brain [23]. In the latter, this restrictive barrier protects the brain from toxins, pathogens, inflammation, injury and disease [24]. Let's remember that the formation and maintenance of these barriers are regulated by glial cells. In the eye, a disruption of this barrier is related to various pathologies, including inflammatory diseases of the eye, retinal degenerative diseases and ocular damage resulting from surgeries, among others.

Beyond this complex structure, new questions arose about the intricate structural organization of the eye. In 2012, Iliff, et al., proposed the existence of a "glymphatic system" in the brain, this being a paravascular pathway for the clearance of interstitial solutes [25]. The brain is adapted to the use of this paravascular pathway, through which fluids can be freely exchanged without crossing the tightly regulated endothelial cell layer [26]. Given the understanding of the retina as part of the CNS, it was theorized that an analogous system might be found in this tissue. In 2015, Denniston and Keane reported that the glymphatic system or at least a paravascular system equivalent to that present in the brain, was found in the retina [27]. Analyzing the work by Errera, et al., the authors stress the value of images obtained from patients with retinal vasculitis, where the presence of the paravascular space could be observed [27,28]. In 2019, Jacobsen, et al., conducted a prospective and observational study of 10 subjects and they confirmed the presence of a CSF marker within the visual pathway. These *in-vivo* findings show a direct communication between the subarachnoid space and the extravascular space of the visual pathway [29].

These findings support the concept of specialized clearance mechanisms within the retina that are similar to those described in the brain. As will be discussed in subsequent sections, impairment of these homeostatic and drainage pathways may contribute to the development of retinal diseases such as glaucoma.

Retinal Disease and Neurodegeneration

As discussed, the retina is a complex system comprising a large number of neurons, supported by a rich network of glial cells. Neurotransmission within the visual pathway is tightly regulated, meaning that small changes in neurotransmitter concentration or in the structure of the optic nerve can have significant consequences. On the other hand, there is increasing evidence of the presence of a glymphatic system in the eye that is analogous to that found in the brain. Failure in this complex drainage system may be the basis for both ocular and cerebral conditions. Below, we will focus on three pathophysiological mechanisms that we believe play a significant role in the development of different neurodegenerative processes, namely: glutamate and excitotoxicity, optic neuritis and demyelination and vascular and glymphatic impairment. As will be discussed later, these converging pathways may represent promising targets for novel therapeutic strategies.

Glutamate and Excitotoxicity

Physiological Role of Glutamate in the Retina and CNS

Glutamate is a complex amino acid that exerts a variety of physiological functions. In the central nervous system, it is the primary excitatory neurotransmitter and a metabolic precursor of GABA, the main inhibitory neurotransmitter [30]. Due to its characteristics as an excitatory neurotransmitter, glutamate has been identified as having a potential role in various types of neuroplasticity mechanisms, such as the regulation of spine density or synaptic reorganization. This gives glutamate a significant role in higher CNS functions, such as cognition, learning and mood [31].

In the retina, glutamate begins to play a major role from an early stage of development. It is essential for the regulation of differentiation and proliferation, as well as cell survival and apoptosis, affecting synapse formation and network maturation in the retina [32].

In the mature retina, glutamate is the primary excitatory neurotransmitter and plays a major role in vertical and horizontal pathways, as well as in ON and OFF pathways. Further details can be found in previous studies in this field [14, 21, 33-35]. Glia plays a vital role in glutamate metabolism. Glutamate must be removed from the entire extracellular space and glutamate uptake is the mechanism responsible for the long-term maintenance of low extracellular concentrations of this neurotransmitter. Glia captures extracellular glutamate and may convert it into glutamine. This is one of the main proposed mechanisms by which glutamate is recycled [36].

Glutamate Excitotoxicity: A Shared Mechanism of Retinal and Cerebral Neurodegeneration

We have seen that glutamate plays a major role in both the retina and the brain. However, a deregulation of this system leads to neuronal damage and death due to the excitotoxicity that this neurotransmitter can generate. Excitotoxicity is considered a key pathological mechanism in various retinal conditions, such as glaucoma, diabetic retinopathy, ischemic retinopathy and other retinal degenerative conditions. Glutamate clearance by glia is essential to prevent this glutamate excitotoxicity [37]. On the other hand, this mechanism plays a key role in CNS conditions, such as schizophrenia, mood disorders and chronic pain, among others [38].

The visual system is susceptible to a wide variety of diseases collectively referred to as retinal degenerative diseases. The accumulation of glutamate in the extracellular space, together with neuronal overactivation, has been implicated as a major contributor to retinal neurodegeneration. Exposure to micromolar concentrations of glutamate can lead to neuronal damage and death [39].

RGCs are particularly vulnerable to increases in glutamate levels, especially due to their high density of dendritic glutamate receptors [40]. RGCs are exposed to different extracellular environments and exhibit non-homogeneous energy demands. In turn, they have high oxygen and energy demands, which makes them susceptible to damage from Reactive Oxygen Species (ROS) production and mitochondrial imbalance [41]. Alterations in the NMDA receptor and mitochondrial impairment have been associated with neurodegenerative disorders. Constant activation of the NMDA receptor has been associated with alterations at the mitochondrial level, such as ROS production, changes in the electron transport chain and altered calcium homeostasis [42]. These mechanisms position RGCs as a primary target for various retinal conditions. As suggested by Muench, et al., RGCs may be the most vulnerable of all neuronal cell types [43].

A similar mechanism of neuronal death occurs in strategic regions of the hippocampus, such as CA1, CA3, the subiculum and the dentate gyrus, with a preference for pyramidal cells. Neuronal damage and disruption of synaptic connections in the mossy fibers in mesial temporal sclerosis are caused by glutamate excitotoxicity [44].

As previously mentioned, glia plays a key role in glutamate physiology. It is therefore not surprising that changes in their function lead to glutamate excitotoxicity. Müller glial cell malfunction leads to changes in glutamate homeostasis, resulting in an increase in glutamate and subsequent collapse of retinal function. Activation of the NMDA receptor affects Müller glial cells and the retinal vasculature, increasing permeability to immune system cells [41]. At the CNS level, endothelial cells have been found to express NMDA receptors which, when overstimulated by glutamate, cause disruption at the Blood-Brain Barrier (BBB) level, leading to immune cell infiltration in multiple sclerosis [45]. In this disease, one of the neurodegenerative mechanisms involved beyond demyelination is glutamate excitotoxicity [46].

Glutamate excitotoxicity is a pathological mechanism that occurs in various retinal disorders. At the same time, this mechanism is involved in different types of brain disorders. This parallelism opens a window to therapeutic possibilities that target this mechanism in the treatment of degenerative retinal diseases and other neurodegenerative processes throughout the CNS.

Optic Neuritis and Demyelination

As we have seen in the anatomy section, the optic nerve is a true tract of the CNS and a bridge between the retina and the brain. It is therefore an extension of the brain parenchyma that is myelinated by oligodendrocytes and sends visual impulses to the brain [47]. This observation has a reason, as it has been estimated that the axons of the optic nerve may constitute up to 38% of all the axons entering and leaving the CNS [48]. An important aspect of the anatomy of this nerve is the presence of unmyelinated portions, where saltatory conduction cannot be performed due to the absence of myelin. Consequently, RGCs generate large amounts of ATP in their axons to repolarize the plasma membrane. For further details on the anatomy and physiology of the optic nerve, we refer the reader to the work by Buonfiglio, et al. [49]. This absence of myelin in these portions of the optic nerve pathway results in a high energy demand for the generation of action potentials, thereby increasing the susceptibility of RGCs to mitochondrial impairment. Myelin has been shown to play a key role in supplying nutrients to the axon, as the entire mitochondrial respiratory chain has been detected in the myelin sheath of the optic nerve. These findings provide a possible explanation for the association between myelin loss and axonal degeneration observed in demyelinating disease [50].

ON is a common diagnosis in clinical practice and is one of the leading causes of visual loss in young adults. It can be defined as a subacute loss accompanied by retro-orbital pain that worsens with eye movements [51]. It is traditionally classified as either typical or atypical ON. Moreover, a new classification of ON based on the anatomical location of the lesion is emerging. We will focus on the anatomical compartments that include pathologies involving the entire CNS, such as Multiple Sclerosis (MS), MOG Antibody-Associated Disorder (MOGAD) and Neuromyelitis Optica Spectrum Disorders (NMOSDs). For further details on this classification and the different causes of ON, we refer the reader to the work by Grecco, et al. [52].

Multiple Sclerosis

MS is a chronic autoimmune disease that affects the CNS. Myelinated axons are the target of MS attacks, which cause varying degrees of structural damage to the myelin and axon [53]. Both cellular components (auto-reactive CD4+ T-cells, B-cells, NK cells, macrophages and microglia) and soluble mediators (IFN-Y, IL-6, immunoglobulin G1, among others) participate in the pathogenesis of this disease [54]. An important aspect of MS lesions is the involvement of the BBB, which may be key to understanding this complex pathology [55]. Chronic active lesions are characterized by microglial activation, oxidative stress, mitochondrial impairment and iron accumulation, all of which contribute to progressive neuroaxonal degeneration [56]. Mitochondrial involvement is an important aspect of MS pathogenesis. Early Wallerian degeneration is accompanied by mitochondrial swelling [57].

Anterior optic pathway involvement is common in demyelinating diseases of the CNS. In MS, ON is the initial presentation in 25% of the cases and affects 70% of patients throughout the course of the disease [58]. As can be seen, ocular disease is extremely common in MS, with variable clinical, pathological and imaging findings. In a study conducted by Green, et al., the eyes of 82 MS patients were histologically evaluated. The findings revealed significant retinal disorders in this pathology, including inner retinal atrophy, decreased RGC populations, inner nuclear layer atrophy, inflammatory cellular infiltrates and perivascular inflammatory cells [59].

As it happens in other parts of the CNS, the retina is exposed to the same pathological mechanisms that perpetuate the disease in the brain. To understand MS in the eye, it is important to consider the anatomy of the optic nerve. We therefore recommend that the reader first reviews section 6 of this paper.

Persistence of the pro-inflammatory state in the optic nerve causes axon loss due to demyelination over time. The function of the axon is directly affected by pro-inflammatory cytokines, enzymes and nitric oxide, produced by activated immune cells in the eye. On the other hand, intra-axonal mitochondrial impairment is perpetuated, causing even more damage to the nerve structure [60-62]. It is worth remembering that glutamate excitotoxicity mechanism is one of the main causes of RGC death in this pathology [40,46].

As we can see, MS is a complex disease in which abnormal activation of the immune system leads to demyelination at different levels of the CNS. ON is a common initial manifestation in MS, leading to retinal functional and structural disturbances. MS is a clear example of a pathology affecting the entire CNS and the retina is no exception. New therapeutic strategies based on neuromodulation and immunomodulation of the inflammatory microenvironment present in MS may offer new treatment options for this complex condition.

Neuromyelitis Optica Spectrum Disorders and MOG Antibody-Associated Disorder

Over recent years, other diagnoses began to play a leading role in demyelinating disorders. We will focus on two of them: NMOSD and MOGAD. These entities introduced a new paradigm and shed light on the complex spectrum of demyelinating diseases.

NMOSD is an inflammatory autoimmune demyelinating disease of the CNS characterized by severe attacks of ON and myelitis [63]. Despite its first description in 1894 by Dr.Eugene Devic, NMOSD was previously considered a subtype of MS and has only recently been characterized as an independent entity. In 2004, the discovery of a circulating IgG autoantibody in patients with NMOSD that was absent in patients with MS changed the paradigm of this disease. Within a year, the astrocyte water channel protein aquaporin 4 (AQP4) was identified as the target of this autoantibody [64].

In NMOSD, the BBB is leaky, allowing inflammatory cells, cytokines and autoantibodies to reach the CNS. The AQP4-IgG autoantibody binds to the extracellular domain of the AQP4 protein of the astrocyte endfeet, resulting in cytotoxicity. In turn, the complement system is activated, leading to astrocyte injury, neuronal damage and secondary demyelination due to cytotoxicity. The cells involved in the pathogenesis are: B-cells, T-cells, neutrophils, eosinophils and microglia [65]. It is worthwhile commenting that central and peripheral tolerance mechanisms are defective in NMOSD [66].

Beyond this microenvironment of autoimmunity and constant inflammation, a mechanism of damage across multiple CNS

conditions can be spotted: glutamate excitotoxicity. The immune mechanism mentioned above prevents astrocytes from capturing free glutamate from the extracellular space, causing excitotoxicity and damage to nerve cells and their structures, such as the myelin sheath. This alteration in glutamate homeostasis promotes myelin destruction and the demyelination characteristic of this pathology [67]. Hinson, et al., highlighted the pathogenic role of NMO-IgG in disrupting glutamate transport, leading to the injury or death of both neurons and oligodendrocytes [68]. On the other hand, Alberdi, et al., demonstrated glutamate sensitization of oligodendrocytes to complement attack as they are extremely sensitive to changes in glutamate concentration [69].

MOGAD is a demyelinating disorder of the CNS that differs from MS and NMOSD. MOGAD refers to a demyelinating syndrome associated with IgG autoantibodies that target myelin oligodendrocyte glycoprotein, a surface protein present in oligodendrocytes and myelin [70]. Unlike NMOSD, where astrocytic injury precedes demyelination, MOGAD is characterized by primary antibody-mediated injury directed against oligodendrocyte-associated myelin proteins. The autoimmunity present in this pathology can be triggered by various factors, which can activate the autoimmune cascade by molecular mimicry, activate autoreactive lymphocytes and the release of chemokines and cytokines. Among these factors, cases of infection and vaccination preceding MOGAD have been documented [71-73]. This triggering of autoimmunity by infectious factors has also been observed in NMOSD [74].

These two conditions demonstrate in detail the complexity of demyelinating pathologies, in which the immune and excitotoxic mechanisms cause the most severe damage. We have seen how the optic nerve is particularly vulnerable to this type of injury due to its complex structure. These observations reinforce the need for therapeutic approaches that address both immune-mediated injury and secondary excitotoxic mechanisms.

Vascular Dysfunction and Glymphatic Impairment

As we anticipated earlier, increasing evidence suggests the presence of specialized clearance mechanisms within the retina that may be similar to those described in the brain. The BRB represents the retinal counterpart of the BBB, sharing structural and functional characteristics which are essential for the maintenance of neural homeostasis. An important concept to highlight is the immune privilege of the eye. Specializations at the molecular, cellular and anatomical levels give the eye a special relationship with the immune system [75]. These establish an immunologically privileged microenvironment in the eye, making it immunologically unique. The eye has mechanisms capable of suppressing inflammation and regulating immune cells [76]. Glia again plays an important role here, as both astrocytes and Müller cells are capable of responding to retinal injury and promoting a neuroprotective effect in the early stages of the retinal pathology, which is then lost due to the chronic activation of these cells, leading to gliosis [77]. The BRB plays a key role that goes beyond this unique property of the eye. It controls the movement of fluids and molecules between the ocular vascular beds and retinal tissue, preventing potentially harmful agents from entering the retina [78]. A disruption in these barrier mechanisms causes a dysregulation of the immune microenvironment throughout the CNS, such as the brain and retina. As a result of this increased permeability, both cellular elements and soluble factors enter the neural tissue and activate inflammatory and neurodegenerative mechanisms, which we highlight, for example, at the level of MS and NMODS pathophysiology. As mentioned above, the concept of the "glymphatic system" began to be discussed at the brain level based on the observations by Iliff, et al., in 2012 [25]. Subsequently, this concept was extended to another part of the CNS: the retina. Based on the work by Denniston and Keane in 2015 and Errera, et al., the concept of a specialized clearance mechanism within the retina that parallels that described in the brain began to be theorized [27,28]. Since then, experimental, imaging and histological evidence has accumulated, expanding our knowledge of the dynamics of this "glymphatic system" and its potential role in retinal conditions. We will focus on glaucoma as a representative condition in which vascular dysfunction and impaired paravascular clearance mechanisms may converge, highlighting its similarities to neurodegenerative processes within the CNS.

Glaucoma and Alzheimer´S Disease: The Glymphatic Theory

The glymphatic system seems to be analogous to the glymphatic system of the CNS, playing a key role in regulating interstitial fluid movement and waste clearance and potentially a role in CNS immunity [79]. This system enables waste clearance through the CSF flow within the subarachnoid and arterial perivascular space, via a glia-dependent system of perivascular channels. Astrocytes equipped with AQP4 in their endfeet encircle the perivascular tunnels within the glymphatic system and support fluid transport [80]. Amyloid β (Aβ) and other neuronal degradation products have adverse effects on synaptic transmission and

can trigger irreversible neuronal damage. Due to the high sensitivity of neurons to their environment, it is essential that waste products of neural metabolism are efficiently removed from the brain interstitial space [81]. Dilation or enlargement of the perivascular spaces, as well as disruption of the BBB, could affect the transport of these waste products to the periphery, thus increasing the risk of neurodegenerative diseases such as Alzheimer's or Parkinson's [82].

On the other hand, the retina is the most metabolically active part of the eye and requires constant clearance of metabolic waste. Like the brain, the retina and the optic nerve lack a traditional lymphatic drainage system. Since the discovery of the glymphatic system in the brain, research and knowledge about this potentially complex drainage system has advanced significantly [83]. In 2016, Wostyn, et al., highlighted a potential contribution of the ocular glymphatic system to the pathogenesis of glaucoma. They proposed the possible existence of a paravascular transport system in the optic nerve. This was based on the fact that this nerve is a tract of the CNS that is surrounded by CSF in the subarachnoid space [84].

Glaucoma is a progressive optic neuropathy characterized by the degeneration of RGCs and resulting changes in the optic nerve. Although this condition is usually accompanied by an increase in Intraocular Pressure (IOP), it can also occur in individuals with normal IOP [85]. In recent years, an association has been suggested between glaucoma and various neurodegenerative diseases, including Alzheimer's disease. It has been proposed that a failure of the glymphatic system may contribute to the poor drainage of Aβ in neurodegenerative diseases as well as in glaucoma [86]. McKinnon, et al., reported that rat RGCs subjected to chronic elevation of IOP exhibit caspase-3-mediated abnormal processing of Aβ precursor protein with increased expression of Aβ [87]. This gives rise to a new mechanism which leads to RGC death involving chronic amyloid-beta neurotoxicity and mimicking Alzheimer's disease at the molecular level [88]. In glaucoma, impairment of glymphatic clearance could occur due to paravascular communication arrest at the site of the lamina cribrosa. It has been suggested that there may be a continuous network of paravascular channels that surrounds the central retinal vessels in the optic nerve and that may serve as drainage channels from the subarachnoid space around the optic nerve to the retina [89].

Other important mechanisms leading to RGC death and loss of vision in glaucoma are: glutamate excitotoxicity, oxidative stress, neuroinflammation, vasoconstriction and autophagy [90]. Alzheimer's disease is a progressive neurodegenerative disorder that affects cognitive functions such as memory, language, learning, behavior and reasoning, significantly interfering with the individual's daily functioning. Pathophysiologically, it is characterized by the formation of neurofibrillary tangles composed of tau protein and extracellular plaques made up of Aβ [91]. As we have recently seen, Alzheimer's disease has been increasingly associated with disruption of the glymphatic system in the brain. The glymphatic system plays a key role in facilitating the drainage of extracellular elements such as proteins, including Aβ, a protein that is essential to the pathogenesis of Alzheimer's disease. Since the studies by Ilif, et al., this paravascular pathway began to gain importance in our understanding of this complex pathology [25]. The misaccumulation of cellular waste products is a recognized phenomenon in various neurodegenerative diseases [92]. Aβ can activate receptors in microglia, leading to the production of proinflammatory cytokines. This inflammation causes Aβ accumulation, resulting in a decreased clearance of this protein. All of this produces changes at the glial cell level, which can cause a decrease in glymphatic flow.

Glial cell involvement gives rise to a mechanism that is common to the different pathologies reviewed: glutamate excitotoxicity and glutamate recycling impairment, which leads to neuronal death. In Alzheimer's disease patients, a decrease in glutamate transporter capacity and protein expression and a selective loss of Vesicular Glutamate Transporter (VGluT) was observed [93].

Glaucoma and Alzheimer's disease are complex pathologies that are difficult to manage and have deep consequences for patients and their environment. These pathologies have been shown to share pathophysiological mechanisms that should not be ignored. Glymphatic impairment, glutamate excitotoxicity, Aβ accumulation and neuronal death are key pathological mechanisms in these diseases. This opens the door to therapeutic strategies that target these mechanisms, allowing for the implementation of therapies able to treat one disease and be also effective to treat the other.

New Perspectives in the Treatment of Retinal Diseases: Stem Cell and Exosome Therapies

Throughout this review, we have explored the complexity of the eye in terms of both its physiology and pathology. Complex mechanisms perpetuate and sustain damage to the retina and these same pathological mechanisms are found across different CNS pathologies. These pathologies can be summarized as conditions involving alterations in neuromodulation and

immunomodulation, as well as the presence of a consistent inflammatory microenvironment that perpetuates damage to neuronal tissue and its structures.

Both retinal conditions and other neurodegenerative diseases of the CNS are complex conditions characterized by a significant disability in the individual and difficult therapeutic approaches. In this context, we highlight stem cell and exosome therapy as a novel therapeutic strategy for this type of conditions. First, we will review general concepts of both stem cells and exosomes and then we will present the properties of these cells and their secretory products that could have a therapeutic value in these pathologies. Finally, we will discuss previous experiences with the use of these therapies in both retinal conditions and other CNS neurodegenerative diseases.

Stem Cells and Exosomes: Key Concepts

Stem cells are undifferentiated cells with the capacity for self-renewal and differentiation into various types of tissue. They interact closely with the immune system and can act on the inflammatory microenvironment present in a large number of pathologies [94]. In turn, they secrete a wide range of active biomolecules such as proteins, nucleic acids, exosomes and microvesicles with paracrine effects that enhance their therapeutic potential [95].

Exosomes are nanoscale extracellular vesicles (30-150 nm in diameter) enclosed by a lipid bilayer and naturally released by cells. They function as key mediators of intercellular communication through the transfer of proteins, nucleic acids, lipids and other bioactive molecules. These vesicles contribute to the maintenance of cellular homeostasis, coordinate tissue-level responses and participate in the regulation of diverse physiological processes [96]. Stem cells have been found to function in a paracrine way through their exosomes. Stem cell- derived exosomes retain many of the therapeutic characteristics of their cells of origin, including anti-inflammatory, immunomodulatory and regenerative effects [97].

As we will see below, both stem cells and exosomes act on the pathological mechanisms present in retinal conditions and other neurodegenerative processes through neuromodulation and immunomodulation.

Neuromodulatory and Immunomodulatory Mechanisms of Stem Cells and Exosomes

Multiple complex pathological mechanisms are found and are interconnected in different retinal conditions and other neurodegenerative processes. Rather than acting in isolation, these processes collectively contribute to progressive neuronal and structural damage. Stem cells and their derived exosomes possess neuromodulatory and immunomodulatory properties that may influence these pathological pathways and may potentially modify the disease microenvironment. An important quality of stem cells that distinguishes them from most cells is their ability to migrate to differentiated tissues. Previous studies have shown the ability of stem cells to migrate to damaged tissue [98,99]. Similarly, exosomes have been shown to cross the BBB, expanding their potential relevance in CNS disorders [100].

Neuroinflammation has emerged as a central driver in the initiation and progression of multiple neurodegenerative conditions discussed in this review. Therefore, strategies capable of modulating inflammatory responses are of particular interest. Several studies have shown that exosomes have anti-inflammatory properties in the CNS. Exosomes may exert neuroprotective effects by protecting neurons from different injuries and supporting oligodendrocytes. On the other hand, they could play a role in modulating glia, leading to the production of neurotherapeutic factors [101]. In demyelinating diseases such as MS, NMOSD and MOGAD, we identified the presence of autoreactive immune cells and soluble mediators that intensify the structural and functional damage to different structures both in the retina and in the rest of the CNS. Through cellular mechanisms (action on Treg lymphocytes, macrophages) and humoral mechanisms (exosomes, secretomes), stem cells exert an immunomodulatory action capable of regulating inflammation and promoting tissue repair [94]. The release of trophic factors together with the suppression of inflammation may also be responsible for the healing effects of stem cells [102]. Autologous stem cells stand out as a novel therapy in these processes thanks to their immunomodulatory properties, low immunogenicity and regenerative capacity [103]. As previously discussed, neurons and glial cells maintain a dynamic bidirectional interaction that is essential for myelination and synaptic regulation. Neurons and glia actively communicate with each other to coordinate axonal growth and myelination and emerging data suggest that exosomes contribute to these processes [104]. This sheds new light on the interrelationship between these two cell types and leads to the search for new therapeutic strategies based on this communication, which may be impaired in neurodegenerative diseases.

Glutamate neurotransmission plays a key role in both the physiology and pathology of the CNS. Glial cells are essential for maintaining glutamate homeostasis. Exosomes could play an important role in communication within the CNS, both locally and remotely. Evidence shows that the production of exosomes by nerve cells is a highly regulated process, in which glutamatergic neurotransmission plays a pivotal role in its regulation [105]. These observations provide further insight into how dysregulated glutamate signaling may interact with extracellular vesicle biology.

A cross-cutting mechanism of cell death and damage that we studied throughout the review is glutamate excitotoxicity due to a disruption in the homeostasis of this neurotransmitter, which leads to mitochondrial dysfunction and damage by ROS. RGCs are susceptible to damage by ROS, which are produced by an impaired mitochondrial function triggered by altered glutamate concentrations, causing neuronal death. This is an essential pathological mechanism in various retinal and CNS diseases.

The ability of stem cells to interact with injured tissue has been extensively investigated. One well-documented mechanism involves the transfer of mitochondria from stem cells to damaged cells. This mitochondrial transfer increases intracellular ATP levels, thereby improving cellular bioenergetics and enhancing functional performance [106]. In injured cells, this mechanism of mitochondrial transfer restores respiration, increases ATP levels and significantly decreases ROS levels [107]. This unique property of stem cells turns them into a potential therapeutic strategy for conditions involving neuronal damage and death due to mitochondrial alterations triggered by glutamate excitotoxicity, such as glaucoma, MS, Alzheimer's disease, ischemic injuries, etc.

Taken together, these mechanisms suggest that stem cells and their derived exosomes may influence multiple interconnected pathological processes involved in retinal and CNS neurodegeneration. In the following section, we will briefly review previous trials involving stem cell-based and exosome-based therapies for retinal and other neurodegenerative disorders.

Use of Stem Cells in Retinal Conditions and Other Neurodegenerative Processes

Over the years, stem cell therapies from different sources have been gaining prominence in the field of retinal pathology and other neurodegenerative processes. Owing to their immunomodulatory and neuromodulatory properties, these therapies are increasingly being explored as potential multi-target interventions in complex neurodegenerative conditions. First, an important point to highlight is the safety profile of adult stem cell application. In a systematic review and meta-analysis of clinical trials, Lalu, et al., reported no significant increase in severe adverse events associated with mesenchymal stromal cell therapy, supporting its overall safety in clinical settings [108].

Regarding retinal diseases, Holan, et al., summarized the experimental and clinical experiences involving stem cell therapy in retinal degenerative disorders, emphasizing mechanisms such as immunomodulation, secretion of trophic and neuroprotective factors, anti-apoptotic effects and neuromodulation [109]. We refer the reader to this text for further discussion on the topic. Similarly, Stern, et al,. explored the therapeutic potential of cell-based strategies in various ocular diseases, emphasizing regenerative and protective mechanisms [110].

The Stem Cell Ophthalmology Treatment Study (SCOTS) has reported observational findings in patients with retinal and optic nerve disorders. Preliminary reports described functional improvement in a single patient case of optic neuropathy treated under this protocol [111]. Subsequent publications reported visual function improvement in cohorts of patients with Leber’s hereditary optic neuropathy and retinitis pigmentosa [112,113]. While these studies suggest potential therapeutic effects, further controlled studies are required to better define efficacy. On the other hand, in other CNS neurodegenerative pathologies, stem cells have also begun to be considered as a potential therapeutic tool. Goldman reviewed different neurodegenerative pathologies that are attractive targets for the use of cell-based therapies [114]. An important point in this work is that it includes the retina as part of the CNS and a target for this type of therapy. We encourage the reader to delve deeper into the subject by reading Goldman's work. Likewise, Deokate, et al., emphasized the capacity of stem cells to modulate immune responses and promote microenvironment favorable for neural repair across multiple neurodegenerative conditions [115]. Finally, our group has explored therapeutic approaches using stem cell and exosome therapy in CNS pathologies. We recently reported functional and structural improvements in a patient with mesial temporal sclerosis after initiating combined stem cell and exosome therapy [116]. We also reported a case of GAD+ autoimmune cerebellar ataxia, focusing on functional and clinical improvements after starting therapy. For a better understanding and further details, we encourage the reader to review the cases [117].

Given the above, we hold that further research into the use of this therapy should be conducted on a larger number of patients with these conditions. This opens up an exciting field in the approach to neurodegenerative processes, where much remains to be learned and investigated in order to make these advances available to patients.

Conclusion

The central focus of this work is the eye, especially the retina, as a vital part of the CNS. During this review, we outline the embryological origin of the retina, which is an evagination of the diencephalon. We also examined the structural similarities between the retina and other parts of the CNS, as well as the vulnerability it shares with the brain in the face of pathological mechanisms that perpetuate damage and neuronal death. Neuroinflammation, glutamate excitotoxicity, mitochondrial dysfunction, blood-tissue barrier disruption and impaired clearance systems such as the glymphatic pathway emerge not as isolated findings, but as interconnected biological processes that go beyond traditional organ boundaries. These findings challenge the classic compartmentalization of retinal conditions and neurodegenerative processes, as well as how their treatment is addressed. Glaucoma and Alzheimer's disease, optic neuritis and multiple sclerosis and other neurodegenerative processes may reflect similar manifestations of shared molecular and cellular disturbances. In this context, therapeutic strategies aimed at modulating the inflammatory microenvironment present in the various pathologies that can occur in the CNS could represent a paradigm shift in the treatment of neurodegenerative processes. Stem cell and exosome therapies offer a biologically plausible, multi-target approach based on immunomodulation, neuromodulation, mitochondrial support and intercellular signaling restoration.

Future progress will depend on integrating advances in neuroimmunology, extracellular vesicle biology, stem cell properties and regenerative medicine into rigorous translational frameworks. The major challenge ahead is to further elucidate the mechanisms that initiate and perpetuate these conditions, thus redefining the therapeutic approach to entities that are usually managed by specialties in isolation. The convergence between the retina and the brain invites a unified vision of CNS physiology and neurodegeneration, one in which the eye is not an isolated structure, but an integral and dynamic component of the same biological system.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was taken for this study.

Authors' Contributions

All authors contributed equally to this paper.

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