DOI: https://doi.org/10.54393/pjhs.v5i10.2267

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 5, Issue 10 (October 2024)

Systematic Review

OPEN ACCESS

The Key Role of Brain-Derived Neurotrophic Factor (BDNF) in Pathophysiology of Glaucoma and Its Therapeutic Potential

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ARTICLE INFO

Keywords:
Brain-derived Neurotrophic Factor, Glaucoma, Neuroprotection, Retinal Ganglion Cells

How to Cite:
Durrani, M. U., Usman, A., Noureen, F., Munim, A., Abbas, S., Bilal Ahmed, Z. ul A., & Khaliq, M. H. (2024). The Key Role of Brain-Derived Neurotrophic Factor (BDNF) in Pathophysiology of Glaucoma and Its Therapeutic Potential: Brain-Derived Neurotrophic Factor (BDNF) in Pathophysiology of Glaucoma. Pakistan Journal of Health Sciences,5(10). https://doi.org/10.54393/pjhs.v5i10.2267

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Received Date: 2nd September, 2024
Acceptance Date: 27th October, 2024
Published Date: 31st October, 2024

ABSTRACT

Glaucoma, a leading cause of irreversible blindness, is increasingly recognized as a neurodegenerative disease affecting broader neuro-ophthalmic pathways. Brain-derived neurotrophic Factor is a crucial neurotrophin, that supports the growth, maintenance, and survival of neurons and has been implicated in glaucomatous damage where its levels are diminished. **Objectives:** To focus on the role of Brain-Derived Neurotrophic Factor in the pathophysiology of glaucoma and its therapeutic potential by enhancing the survival of retinal ganglion cells. **Methods:** The studies in this review are taken from well-known public libraries for scientific research such as PubMed (60%), Science Direct (25%) and Springer Link (15%), in line with PRISMA guidelines. Various works conducted over the past decade from different parts of the world, including North America, Europe, and Asia, have provided evidence that the augmentation of Brain-Derived Neurotrophic Factor signalling may be a very effective approach to managing or halting the progression of glaucomatous optic neuropathy through neuroprotection and improving retinal ganglion cells survival. **Results:** Studies in both animals and humans indicate that Brain-Derived Neurotrophic Factor and its downstream signals promote the survival of retinal ganglion cells and decrease the extent of apoptotic cell death, oxidative stress, and inflammation in glaucoma. Moreover, enhancements of Brain-Derived Neurotrophic Factor neuroprotective effects are supported by factors such as Nerve growth factor and Brain-Derived Neurotrophic Factor. **Conclusions:** It was concluded that Brain-derived neurotrophic Factor has the potential to be used as a diagnostic marker for Glaucoma as well as it could be evaluated for its therapeutic potential against the disease.

INTRODUCTION

Glaucoma, a progressive neurodegenerative eye disorder, is one of the leading causes of irreversible blindness worldwide. It involves the degeneration of retinal ganglion cells (RGCs) and optic nerve damage, leading to gradual vision loss. Primary open-angle glaucoma (POAG) is the most common form, accounting for over 74% of glaucoma cases globally, particularly in populations with genetic predispositions [1]. The primary internal cause of glaucoma is increased intraocular pressure (IOP), but optic nerve damage can occur even in the absence of elevated IOP, a condition termed normal-tension glaucoma [2]. Recent studies have shown that brain-derived neurotrophic factor (BDNF), a neurotrophin essential for neuronal survival and synaptic plasticity, plays a significant role in the pathophysiology of glaucoma [3]. Brain derived neurotrophic factor (BDNF) is an essential protein mediating neuronal survival, maintenance and function especially in the central nervous system with a defined role for retinal ganglion cells (RGCs), important in glaucoma. Activation of such signaling pathways (e.g., PI3K/Akt and

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MAPK/ERK) as a consequence of BDNF binding to TrkB receptor protects neurons from apoptosis, oxidative stress and inflammation. Weakness of this protective effect from BDNF reduction can contribute to RGC death and optic nerve damage and hence accelerate vision loss in glaucoma. Preservation of RGCs may be achieved by enhancing BDNF, and BDNF may be a promising target for neuroprotective interventions. Safeguarding RGCs from degeneration by such therapies as direct BDNF delivery, gene therapy to increase BDNF expression, or the use of TrkB agonist to slow glaucoma progression could be the aim of such therapies. Decreased BDNF levels have been associated with RGC death, making BDNF a promising biomarker and therapeutic target for early diagnosis and treatment [4]. Globally, the prevalence of glaucoma varies significantly by region, with Africa, Asia, and the Caribbean reporting the highest rates. African Americans have a 3-4 times higher risk of developing glaucoma than Caucasians [5]. Furthermore, Asia, particularly China, has seen an alarming rise in glaucoma cases due to population ageing and environmental risk factors [6]. In Middle Eastern countries, a study has found no significant association between BDNF polymorphisms and glaucoma progression, highlighting possible regional genetic differences [7]. These regional disparities underscore the need for more population-specific studies and targeted interventions. Brain derived neurotrophic factor (BDNF) is an essential protein mediating neuronal survival, maintenance and function especially in the central nervous system with a defined role for retinal ganglion cells (RGCs), important in glaucoma. Activation of such signaling pathways (e.g., PI3K/Akt and MAPK/ERK) as a consequence of BDNF binding to TrkB receptor protects neurons from apoptosis, oxidative stress and inflammation. Weakness of this protective effect from BDNF reduction can contribute to RGC death and optic nerve damage and hence accelerate vision loss in glaucoma. Preservation of RGCs may be achieved by enhancing BDNF, and BDNF may be a promising target for neuroprotective interventions [8]. Safeguarding RGCs from degeneration by such therapies as direct BDNF delivery, gene therapy to increase BDNF expression, or the use of TrkB agonist to slow glaucoma progression could be the aim of such therapies. Studies also suggest that environmental triggers like UV exposure, pollution, and lifestyle factors (e.g., high blood pressure) can exacerbate glaucoma progression [9, 10].

This systematic review aims on understanding the role of Brain Derived Neurotrophic Factor (BDNF) in pathophysiology and management of glaucoma. Retinal Ganglion Cell (RGC) neurodegeneration is the leading cause of irreversible blindness worldwide and is the hallmark of Glaucoma, a significant public health problem. Currently, traditional therapies have been aimed at lowering intraocular pressure (IOP), but they do not completely combat the neurodegenerative side of the disease. Studies suggest that BDNF can be potential candidate for therapeutic treatment against this disease. This study systematically reviews the current evidence to elucidate BDNF's potential as a biomarker for early diagnosis and a therapeutic agent to preserve RGCs. BDNF's neuroprotective role may be highlighted for innovative treatment approaches targeting the underlying neuronal degeneration in glaucoma other than IOP control.

METHODS

The PRISMA guidelines 2020 for reporting were followed in this systematic study. It included 79 articles in English from last 11 years (2013-2024). The papers included the following information, which was arranged systematically according to the inclusion criteria of PRISMA: author name followed by year, country, sample population, factors and variables, study design, and references. Several search engines, databases and public libraries were included i.e. PubMed, Science Direct and Link Springer. Search was conducted using phrases such as glaucoma, optic disorder, BDNF, signalling pathways of BDNF and retinal ganglion cells survival. Article searches were done using keywords: glaucoma, BDNF, neurotropic factors, retinal cells etc. Initially, all papers which contained glaucoma and BNDF as keywords were taken including the duplicates and abstracts but gradually were filtered out using inclusion and exclusion criteria. We designed the inclusion criteria for this systematic review to identify the most relevant and highest quality studies of BDNF in glaucoma. However, to elucidate the neuroprotective potential of BDNF in preclinical and clinical settings, only experimental, observational and clinical studies that included animals models or humans modes with glaucoma, were taken into consideration. In order to elucidate the therapeutic relevance of BDNF, only those studies examining its direct effect on RGC survival, neuroprotection and signaling pathways were included on the basis of direct effect on RGC survival, neuroprotection and signaling through the BDNF-TrkB pathway. Studies were undertaken to produce results that could reliably report measurable outcomes relevant to glaucoma pathophysiology, such as apoptosis, oxidative stress or inflammation, and that were directly applicable to BDNF's protective role. Excluded articles were the ones which did not contain glaucoma and BDNF linked with each other, were duplicates, were not right kind of methodology i.e. other than clinical, observational and experimental based, which did not come under the range of years selected for study, which was not relevant to the pathology of glaucoma and did not meet the inclusion criteria and thus were eliminated in the filtering process. Inclusion criteria also focused on BDNF as an important factor in tackling the pathophysiology of glaucoma. 79 articles in total were downloaded from databases, 5 duplicates were removed and 74 were left for further study analysis. After a full-text review, a total of 16 articles for the systematic review were included. Due to strictness in inclusion criteria, the majority of the articles taken in the initial steps were removed and only 16 were taken.

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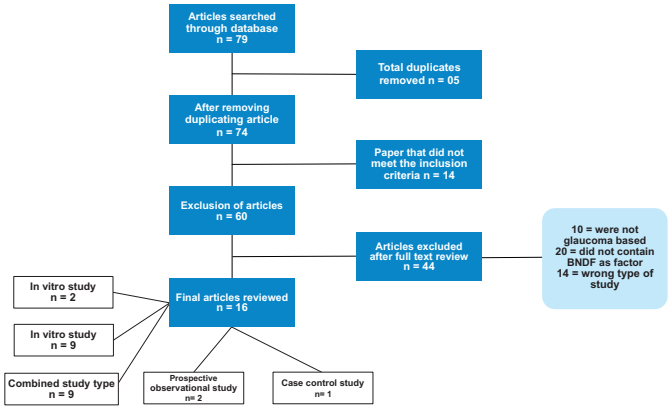

Figure 1: PRISMA Work Flow for filtering out articles focusing on inclusion and exclusion method. Initially, 79 studies were taken according to abstract and title and relevancy. All duplicates were eliminated. Only full-text articles that can be downloaded and read were screened. Finally, 16 studies were taken and sorted according to study type.

RESULTS

The studies in this review are taken from well-known public libraries for scientific research such as PubMed (60%), Science Direct (25%) and Springer Link (15%), in line with PRISMA guidelines. 9 studies focused on in vivo experiments, 2 were focused on in vitro experiments, 2 were focused on in vitro and in vivo combined 2 were focused on the prospective observational study and only one was a case-control study. Results of these studies [12, 16-27] are shown in table 1.

Table 1: Systematic Summary of Articles with In-vitro and In-vivo Study Type, Sorted and Filtered out after Keen Inclusion Criteria

Reference	Study Population (MeanAge in years ± SD)	Study Methodology (Sample Size, N)	Study Variables	Key Findings
[11]	7 months old DBA/2J mice	In vitro, in vivo study	*BDNF, NGF*, CNTF, GDNF	*BDNF and NGF* are important for retinal ganglion cell survival.
[12]	2- to 3-month-old Thy-1-YFP transgenic mice	In vivo study (30 rats)	*BDNF, TrkB, PI3K, ERK1*	*BDNF* and the signalling pathways associated with it have a significant role in preventing retinal ganglion cell death in glaucoma.
[13]	plp1 tg/– mice of 2 months old	In vivo study	*BDNF*, CRMP2	The *AAV2-BDNF* regimen was more effective in the survival of retinal ganglion cells than other regimens.*BDNF* provided greater protection against myelin decomposition.
[14]	DBA/2J mice	In vivo and clinical study	*NGF, BDNF*, NT-3, NT-4 /5,GDNF, CNTF	Neurotropic factors successfully protect ganglion cells of the retina from degradation.
[15]	7 to 8 weeks old male Sprague Dawley rats	In vivo study (130 rats)	*BDNF*	BDNF significantly upregulated the molecules involved in synaptic changes. *BDNF* reduced apoptosis of retinal ganglion cells and enhanced synaptic plasticity in the retina
[16]	Mice (5 months and 1 year old)	In vivo study (N varied by experiment)	*BDNF levels, intraocular pressure (IOP) ,amyloid β levels, ganglion cell layer (GCL) density, pSTR amplitude*	BDNF significantly upregulated the molecules involved in synaptic changes. *BDNF* reduced apoptosis of retinal ganglion cells and enhanced synaptic plasticity in the retina
[17]	Atoh7 mutant mouse (postnatal)	In vitro , in vivo and clinical study	*BDNF, NGF*, CNTF, TrkB	*BDNF* is important for survival of retinal ganglion cells. *BDNF* can act as potential biomarker to detect glaucoma due to its lower levels during decease. *BDNF* has potential to act as therapeutic agent and neuroprotective agent.
[18]	3 months old mice	In vivo study (48 mice)	S1R, *BDNF*	S1R activation increased the expression of *BDNF*.S1R and *BDNF* visual function in mice.
[19]	Mice models	In vivo study	*BDNF. NGF.* GDNF, tACS	NTF deprivation is linked to apoptosis of retinal ganglion cells in glaucoma. NTF supplementation improves survival of retinal ganglion cells in animal models.
[20]	Glaucoma rat model	In vivo study (39 rats)	*BDNF.* TrkB	AAV2-BDNF therapy protects retinal ganglion cells in glaucoma. BDNF restores TrkB receptor levels providing long-lasting protection.

DOI: https://doi.org/10.54393/pjhs.v5i10.2267

[21]	9-week-old male Sprague rat model	In vivo study (42 rats)	*BDNF, caspase-3, Aβ1-40, TrkB, ERK1/2*	Aβ1-40 apoptosis was suppressed by *BDNF* treatment which helped in the survival of ganglion cells in the retina.
[22]	Retinal cells of animals	In vitro study	*BDNF . GDNF*	The combination of GDNF and *BDNF* increased the survival of ganglion cells of the retina by 70%.
[23]	7 months old DBA/2J mice	In vivo study (15 mice)	*BDNF PIGF, VEGF-A, IL-6,IL-1β, 1,25(OH) 2D3*	1,25(OH)2D3 reduced inflammation, preserved retinal ganglion cells and increased expression of *BDNF*.

Patients-based studies, Sorted and Filtered Out After Keen Inclusion Criteria are shown in table 2.

Table 2: Systematic Summary of Patients-Based Studies, Sorted and Filtered Out After Keen Inclusion Criteria

Reference	Study Population (Mean Age in years ± SD)	Study Methodology (Sample Size, N)	Study Variables	Key Findings
[24]	Patients with glaucoma in different stages. mean age 66 ± 11.3	Case-control study	*BDNF*, NGF	Lower *BDNF* and *NGF* levels were observed in patients having advanced glaucoma.
[25]	27 patients with glaucoma (mean age of 65.8 ± 12.2)	Prospective observational study (78 patients)	*BDNF*, IOP, MD, PSD, GCC	Lower level of BDNF (7.2 ± 3.6 ng/mL) in serum of patients with glaucoma.*BDNF* levels vary in different stages of glaucoma.
[26]	Patients with two distinct glaucoma stages (mean age 72.0 ± 10.1 years.)	Prospective observational study (43 patients and 62 eyes)	*BDNF*,	*BDNF* was low or undetectable in most cases (21 of 46 eyes in exp).*BDNF* values were 0.034 pg/mL in glaucoma patients, lower than normal.

It is prominent that after critically analyzing different studies, BDNF has been identified as an essential biomarker in neurodegenerative ailments including glaucoma, an ailment which is marked by death of retinal ganglion cells or RGCs. Reduced BDNF levels in patients with glaucoma with progression from less severe to more severe stages of the disease observed. BDNF is involved with the survival of neurons and is also responsible for the sustaining and functioning of these neurons was shown to be involved with reduced levels of neuronal cell death as well as undesirable neuronal dysfunction associated with glaucoma. Furthermore, because BDNF concentration appears to decrease with progression of glaucoma, assessment of low levels of BDNF may enable early intervention and possibly halt onset of the disease and vision loss. Apart from and over and above its uses as a biomarker, BDNF and other NTFs like NGF, GDNF, as well as CNTF have proved to ascertain considerable neuroprotective potential in both experimental glaucoma in animals and human clinical trials. These factors are necessary for the survival of retinal ganglion cells, and the replenishment of these factors has been known to prevent the ramifications of neurodegeneration.

DISCUSSION

This study achieved its aim to explore the involvement of brain-derived neurotrophic factor (BDNF) in the pathophysiology of glaucoma and to highlight its significance in terms of neuroprotection and potential treatment strategies such as synergistic therapy. Glaucoma, a neurodegenerative disease characterized by the progressive loss of retinal ganglion cells (RGCs) and optic nerve damage, remains a leading cause of blindness worldwide. The study primarily focuses on the role of BDNF in maintaining neuronal health, especially in retinal cells, and examines how its dysregulation contributes to the disease's onset and progression [27]. In recent years, an increasing body of evidence has suggested that Neurotrophins like BDNF are not only integral to neuronal survival but may also serve as early biomarkers for neurodegenerative diseases such as glaucoma [28, 29]. Multiple risk factors contribute to glaucoma development and progression. Elevated intraocular pressure (IOP) is one of the most widely recognized internal risk factors [30]. However, it is increasingly acknowledged that glaucoma can occur even in individuals with normal IOP levels, especially in cases of normal-tension glaucoma. External factors, such as age, ethnicity, genetic predispositions, and environmental influences, also play a crucial role [31]. Age-related changes in vascular dynamics, oxidative stress, and inflammation contribute to retinal ganglion cell death by interrupting neurotrophic support, including BDNF signalling [32]. Ethnicity and geography are important determinants of disease prevalence. African Americans, for instance, have a significantly higher risk of developing glaucoma than Caucasians, possibly due to genetic predispositions and socio-environmental factors. In Asian populations, particularly in China, glaucoma is on the rise, driven by both genetic susceptibility and increased environmental pressures such as air pollution and ultraviolet (UV) exposure [33,34]. These findings indicate that while glaucoma may have a common pathway in terms of retinal cell degeneration, regional variations in risk factors suggest that prevention and treatment strategies

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must be customized based on demographic data [35]. The central nervous system (CNS) plays a pivotal role in the pathophysiology of glaucoma. Brain regions such as the superior colliculus and lateral geniculate nucleus are responsible for processing visual information, and damage to these areas can lead to visual impairment. BDNF, primarily synthesized in the CNS, is vital for neuronal survival and synaptic plasticity [36]. BDNF, being neurotrophic to CNS neurons, interferes with the TrkB receptor that in turn controls critical intracellular signalling cascades needed for RGC survival in glaucoma. Among these, the PI3K/Akt pathway is of special importance since BDNF-TrkB binding can activate Akt, which in turn can phosphorylate anti-apoptotic proteins and protect cells against oxidative stress and inflammations which are crucial in glaucomatous pathogenesis. When the MAPK/ERK pathway is activated, and contributes to the additional perk of enhancing the transcription of genes that offer neuroprotection to RGCs. Collectively, these signalling pathways indicate that BDNF has the potential to be therapeutically used to counteract RGC apoptosis in glaucoma patients. In the context of glaucoma, BDNF is transported from the brain to the retina, where it binds to its high-affinity receptor, TrkB, on retinal ganglion cells. This interaction promotes cell survival by activating various intracellular signalling pathways, including the PI3K/Akt and MAPK/ERK pathways [37]. However, under glaucomatous conditions, this neuroprotective mechanism is disrupted. Elevated intraocular pressure, oxidative stress, and inflammation can lead to reduced BDNF levels in the retina, exacerbating retinal ganglion cell apoptosis [38]. Previous animal studies have implicated BDNF and its receptor, TrkB, in critical roles in RGC survival under glaucomatous conditions. For example, studies of rodent models with induced glaucoma have demonstrated that the administration or gene therapies that increase BDNF expression can significantly reduce RGC apoptosis in these mice and rats. In DBA/2J mice, BDNF application has been demonstrated to initiate the TrkB receptor and protect RGCs through intracellular pathways, including the P13k/Akt and MAPK/ERK cascades, the latter both known to prevent apoptosis and promote survival [12,15,24]. BDNF has also been seen to decrease oxidative stress and inflammation in the retina, caused by glaucoma. In some studies, BDNF mimetics, such as 7,8-dihydroxyflavone, have also been used to study the ability of these to activate TrkB and to mimic BDNF's neuroprotective effects opening them up to noninvasive therapeutic approaches. Furthermore, studies in humans have shown that even in patients with normal IOP, disruptions in BDNF signalling can occur, highlighting the importance of neurotrophic support in maintaining retinal health beyond pressure regulation [39]. This makes BDNF a crucial player in glaucoma progression, particularly in patients who do not exhibit elevated IOP [40]. Several genetic polymorphisms have been linked to glaucoma susceptibility, particularly in genes related to neurotrophic factors like BDNF. For instance, polymorphisms in the BDNF gene may affect the protein's expression and functionality, potentially compromising its neuroprotective role in the retina [41]. A study conducted in Egypt revealed no significant association between BDNF gene polymorphisms and the progression of primary open-angle glaucoma (POAG), suggesting that regional and ethnic variations may play a role in genetic predisposition. Nonetheless, further research is required to fully understand how these genetic factors interact with environmental and lifestyle risk factors in different populations [42]. While this review highlights the significance of BDNF in glaucoma pathophysiology, it also has certain limitations. Firstly, although substantial preclinical evidence supports the neuroprotective role of BDNF, human clinical trials are still in the early stages. Furthermore, the heterogeneity in glaucoma etiology across populations suggests that treatments targeting BDNF may not be universally applicable. Additionally, the impact of regional differences, such as dietary habits, UV exposure, and pollution levels, on BDNF levels and glaucoma progression remains underexplored. Despite the limitations, the study underscores the importance of BDNF as a potential biomarker and therapeutic target for glaucoma. Conventional treatments focus on lowering IOP, but recent advances in neurobiology suggest that neurotrophic factors like BDNF may hold the key to halting or even reversing RGC degeneration. BDNF-based therapies, such as exogenous BDNF delivery, gene therapy to enhance BDNF expression, and small molecules like 7, and 8-DHF that mimic BDNF activity, show promise in animal models.

CONCLUSIONS

It was concluded that investigations into BDNF's pathophysiologic mechanisms have a predominant therapeutic link to glaucoma management particularly its function of protecting the retinal ganglion cells. As such, targeting the BDNF signalling pathways may develop additional therapeutic approaches which can bring about superior safeguard to the nerve cells, given the roles of BDNF and its receptors in the pathogenesis of glaucoma. Early detection of glaucoma through innovative diagnostic tools that measure BDNF levels could allow for timely intervention, particularly in high-risk populations.

DOI: https://doi.org/10.54393/pjhs.v5i10.2267

Additionally, lifestyle modifications that reduce oxidative stress and inflammation, such as a healthy diet rich in antioxidants, may help slow disease progression.

Authors Contribution

Conceptualization: MUD, AU, FN
Methodology: MUD, AU, FN, AM, SA, ZUABA, MHK
Formal analysis: MUD, AU, FN
Writing review and editing: SA, ZUABA, MHK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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