

THE ROLE OF CITICOLINE IN OCULAR NEURODEGENERATIVE DISEASES

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review paper

Summary

Ocular neurodegenerative diseases such as glaucoma, diabetic retinopathy and age-related macular degeneration are the most common retinal diseases causing visual impairment and blindness in the working age elderly population in developed countries. Conventional therapy is either used in an advanced stage of the disease or is not sufficient on its own. Therefore, new treatment modalities are sought, especially in the earlier stages of the disease, in order to prevent disease progression before visual acuity is impaired, and patient's quality of life is altered. Neuroprotection is increasingly popular term used not only to describe the pathology of the central nervous system, but also eye diseases. One of the proposed neuroprotectors of the eye is citicoline. This review provides comprehensive data on the use of citicoline in the most common ocular neurodegenerative diseases.

Keywords: neurodegeneration; neuroprotection; citicoline; eye; brain

Introduction

Human eye is composed of three concentric and distinct layers of tissue: the sclera, the uvea, and the retina. It is a laminar tissue containing neurons and glial cells that plays the crucial role of phototransduction, the process of converting light energy into encoded neural signals delivered to the brain (Ptito et al., 2021). The eye is rightly considered as an extension of the brain because both organs are composed of nerve cells and are derived from the neural tube. The eye provides a unique window to the brain due to its special connection by the retina, a photosensitive nerve tissue that covers the inner surface of the eye, which is properly considered as a part of the brain. Light passes through the cornea, pupil, lens, and vitreous humor and reaches the retina, generating visual stimuli from the outside world, which are converted into electrical impulses and transported through the optic nerve to the brain. The brain interprets them to create a meaningful image. Therefore, the retina is a functional unit of the central nervous system that converts light signals into nerve impulses, and is physically connected to the brain via the axons of the optic nerve.

Chronic progressive neurodegeneration of the retina, which can occur in older adults, can lead to various eye disorders such as glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR). In the elderly population mainly, but also among younger people, this type of eye pathology is the cause of irreversible vision damage or loss (Figure 1).

Typical neurodegenerative diseases of the central nervous system (CNS) are a group of diseases with common characteristics and an etiology that is not fully understood; some risk factors have been identified, but they are not sufficient to explain all observed cases. Furthermore, several studies have shown that ocular disorders also represent features of neurodegenerative diseases, and on the other hand, CNS diseases, such as Alzheimer's disease and Parkinson's disease, show specific changes in the eye (Marchesi et al., 2021).

The most well known, widespread, and common diseases among the elderly population are Alzheimer's disease and Parkinson's disease, which affect more than 30 million and 5 million people worldwide, respectively. For some time, science has been studying whether retinal neurodegeneration can be a predictive factor for Alzheimer's disease and Parkinson's disease and found the changes in the microvasculature of the retina causing retinal thinning (Marchesi et al., 2021) or retinal nerve fiber layer thinning (Guidoboni et al., 2020). Of particular interest is that Alzheimer's disease and age-related macular degeneration share the same biomarkers (Marchesi et al., 2021).

Other neurodegenerative diseases of the CNS are also associated with eye damage, such as multiple sclerosis and amyotrophic lateral sclerosis (Soldatov et al., 2021; Marchesi et al., 2021). Evidence suggests that the cause of DR is not only microvascular damage and that retinal neurodegeneration is a critical component of its development (Mavija, 2020).

The eye - especially its parts such as the retina and the optic nerve represent an extension of the CNS. These

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parts of CNS are the only one that can be seen non-invasively (by fundus examination). Markers of retinal neurodegeneration are associated with markers of brain atrophy, therefore certain diagnostic methods such as optical coherence tomography (OCT) of the retina can also provide information about neurodegeneration in the brain (Mutlu et al., 2017). The incidence of neurological diseases increases dramatically with age, but as life expectancy increases,

the demand for high quality of life in older age becomes a priority for today's health care. Early diagnosis and optimal monitoring are critical for better disease management and to delay progression and disability. It is obvious that neurological and ophthalmological neurodegenerative diseases share underlying biology and pathophysiology which means that they share certain diagnostic biomarkers as well as therapies, especially in the form of neuroprotection.

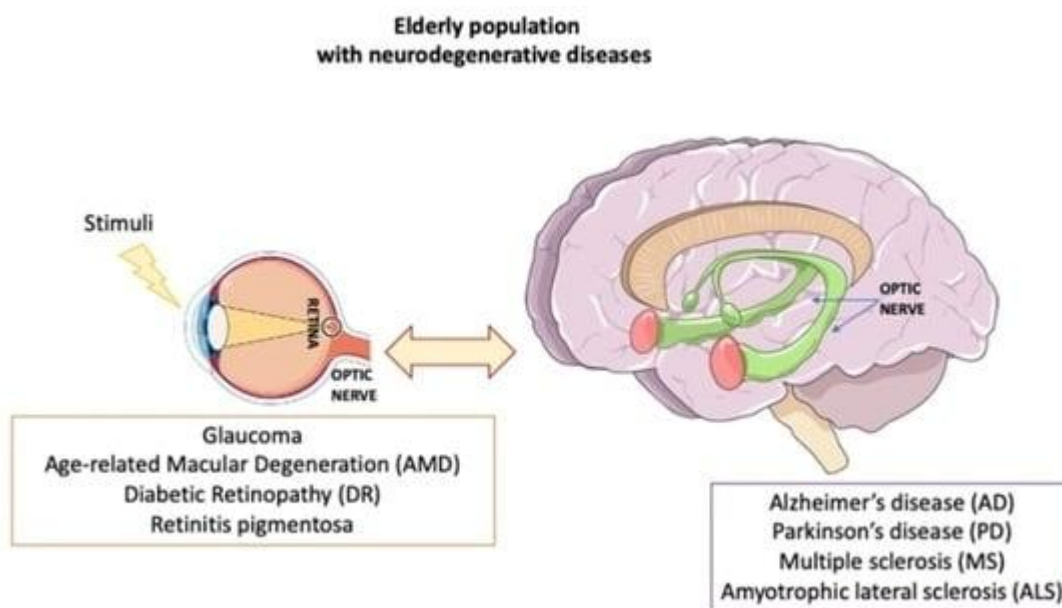


Figure 1. The most common ocular and brain neurodegenerative diseases (Marchesi et al., 2021)

Citicoline: chemical properties and health benefits

Citicoline is the international name for cytidine-diphosphocholine (CDP-Cho).

It is not typically found in food, but is formed in the body when choline combines with cytidine.

Citicoline is a precursor of both phosphatidylcholine, contributing to the synthesis of structural phospholipids in cell plasma membranes, and acetylcholine, an important neurotransmitter in cell metabolism (Garcia-Lopez et al., 2023).

While choline is an essential nutrient, the citicoline level may increase when taking food rich with choline (Table 1). Total choline content is higher in foods of animal origin, compared to foods of vegetable origin (Wiedeman et al., 2018). Upon oral intake, citicoline is thought to be rapidly absorbed and then hydrolyzed to choline and cytidine in the intestinal wall and liver: therefore, besides providing the metabolic precursors of phospholipids, enters synthetic pathways of nucleic acids, proteins, and acetylcholine (Weiss, 1995).

Citicoline can be used in food supplements aimed at a target population of middle-aged to elderly adults at a maximum level of 500 mg/day, and in dietary foods for special medical purposes with a maximum dose of 250 mg per serving and with a maximum daily consumption level of 1000 mg from these types of foods (Synoradzki and Grieb, 2019).

Whereas there is no nutrition or health claim authorized for cytidine either, there are three such claims authorized for choline. The first two state that choline contributes to normal lipid metabolism and to the maintenance of normal liver function and the third claim, stating that choline contributes to normal homocysteine metabolism (Synoradzki and Grieb, 2019). It is extensively researched for its other health benefits in neurology, ophthalmology and psychiatry. Citicoline is widely available as a dietary supplement in a form of tablets, an injection, oral formulation and topical solution for ocular use (Jasielski et al., 2020; Garcia-Lopez et al., 2023). In neurology, citicoline is known as a “procognitive” form of choline used in the prevention of dementia progression, improve memory

and cognitive function, reduce neuropathic pain and accelerated nerve regeneration, and improves prognosis after stroke (Jasielski et al., 2020; Synoradzki and Grieb, 2019; Bonvici et al., 2023; Turana et al., 2021).

Table 1. Food sources of choline (modified from Wiedeman et al., 2018)

Animal source	Plant source
Beef	Nuts (almonds)
Egg	Broccoli
Salmon	Beans
Pork	Red potato
Chicken	White rice
Milk	

The role of citicoline in ocular neurodegenerative diseases

The main ocular neurodegenerative disease include glaucoma, AMD, diabetic retinopathy, anterior ischemic optic neuropathy (NAION) and Retinis pigmentosa.

Although conventional medicine has seen substantial progress in recent years, there is a growing interest in nutraceuticals, bioactive compounds derived from natural sources such as plants, fruits, and cereals, due to their potential therapeutic applications. As it mentioned before the use of citicoline as a supplement is conducted in neurology, ophthalmology and psychiatry.

Citicoline was widely studied in systemic neurodegenerative diseases, like Alzheimer's disease, Parkinson's disease, and brain ischemia. The rationale for the use of citicoline in the aforementioned conditions based on its multifactorial mechanism of action (Oddone et al., 2021).

Glaucoma

Glaucoma is a degenerative neuropathy affecting the retinal ganglion cells. Currently it is the second leading cause of blindness worldwide and the third leading cause of visual impairment. The degeneration of these cells causes progressive optic atrophy that can lead to a complete loss of vision (Starvaggi et al., 2025). The major risk for glaucoma is increased intraocular pressure (IOP). Although the main therapy is conventional, such as the use of topical medicine in the form of drops and/or laser therapy, adjuvant therapy is also used in order to achieve better neuroprotection. The mainstay of current glaucoma therapy is limited to lowering IOP; however, controlling IOP in certain patients can be futile in slowing disease progression. The

understanding of potential biomolecular processes that occur in glaucomatous degeneration allows for the development of glaucoma treatments that modulate the death of retinal ganglion cells and neuroprotection is currently the most important (Kuo and Liu, 2022).

Citicoline has been used to preserve the optic nerve since 1989 when it was used as an intramuscular injection. Today, citicoline is used in the form of drops and in the form of an oral solution in patients with eye problems and its important place in preserving the optic nerve, especially when it comes to the patient's field of vision (Giraldi et al., 1989).

Experimental studies have shown that citicoline may increase the synthesis of phospholipids in the CNS and has a neuromodulator effect, potentially leading to a protective effect on retinal ganglion cells, but also a multicenter study on oral citicoline supplementation in patients with progressive glaucomatous visual field loss found a reduction in the mean rate of visual field progression from -1 dB/year to $-0.15 (\pm 0.3)$ dB/year over a 2-year period (Starvaggi et al., 2025). A randomized placebo clinical trial shown that additional treatment with citicolinedrops to IOP-lowering treatment might reduce disease progression in patients with progressing glaucoma despite intraocular pressure ≤ 18 mm Hg from $1.86 \mu\text{m}$ of RNFL in 3 years in citicoline group, versus $2.99 \mu\text{m}$ in the placebo group (Rossetti et al., 2020).

Anterior ischemic optic neuropathy (AION)

AION is the most common type of acute optic neuropathy in subjects that were aged more than 50 years, due to a deficit of blood supply to the optic nerve from the posterior ciliary arteries. It represents an ophthalmological emergency, which is characterized by sudden and severe visual loss, visual field deficit, peripapillary hemorrhages, and optic nerve head swelling. AION can be non-arteritic (NAION) or arteritic (AAION), with a different prognosis, commonly being NAION, a self-limiting process accompanied by a partial resolution of the visual loss, and leading AAION to a more detrimental impairment of vision up to blindness (Odonne et al., 2021).

Unilateral optic disc edema and abrupt, painless vision loss are its defining features. It is commonly assumed that NAION is caused by an ischemic infarction of the optic nerve head, and, although the exact pathogenesis is still unknown. NAION occurs generally in patients older than 50 years who have small optic discs and vasculopathy risk factors. Even though numerous treatment options have been

proposed, no available effective medical or surgical therapy or prophylactic measure currently exists (Salvetat et al., 2023).

Visual loss in NAION is typically acute and stable, although a further worsening in the first days after presentation is not uncommon; however, the clinical course of NAION stabilizes within a few weeks, at most in 2–3 months, in the majority of patients. But it has a bad prognosis: it results in permanent vision loss, with 40–50% of patients having significant visual impairment or being legally blind in the affected eye (Salvetat et al., 2023).

Regarding the pharmacological management, it is generally accepted that systemic steroid therapy during early stages of NAION has a significant beneficial effect for visual outcome (Odonne et al., 2021; Hayrey et al., 2001; Al-Zubidi et al., 2014). Considering that retinal ganglion cells death is the final consequence of the ischemia in NAION eyes, neuroprotection strategies have been suggested as a potential treatment (Salvetat et al., 2023). Neuroprotective treatments have been reported to counteract secondary neurodegeneration of retinal ganglion cells and their axons used in appropriate interval and the rationale of neuroprotection in NAION resides in the fact that not 100% of the axons of the optic nerve die during an ischemic process, but only a portion of them is damaged. The surviving axons belonging to not damaged retinal ganglion cells, which are responsible for the residual visual acuity and visual field (Odonne et al., 2021).

Parisi et al. (2019) concluded improvement in visual acuity, visual field, VEP and retinal nerve fiber layer thickness after administration of citicoline 500 mg/day in the form of oral solution for six months in NAION patients.

Diabetic retinopathy (DR)

Diabetic retinopathy is the leading cause of new cases of blindness in patients with diabetes mellitus. In 2020, more than 103 million individuals with diabetes mellitus worldwide were affected by diabetic retinopathy, and estimates suggest this number will increase to 160 million by 2045 (Chong et al., 2024). DR represents one of the most important complications of diabetes and preventable causes of visual impairment among people of working age and industrialized countries (Oddone et al., 2021).

Due to constant and long-term elevated blood sugar levels, damage occurs to the small blood vessels of the retina, at the level of precapillary arterioles, capillaries and postcapillary venules. Changes in the fundus occur due to microvascular occlusion - the closure of these blood vessels, which results in

ischemia (lack of oxygen) in the retinal tissue, and are manifested by capillary drop-out and neovascularization (new "unhealthy" blood vessels). These changes in the fundus progress further with the duration of the disease, but also by other factors in and outside the eye that contribute to the development of the disease (Mavija, 2020). In diabetes, vision loss also occurs due to leakage (leakage) from small blood vessels, which is manifested in the fundus as edema (swelling) of the macula. Therefore, diabetic macular edema occurs due to the accumulation of fluid within the layers of the retina in the center of macula lutea (fovea) and/or in its vicinity. It can occur as part of diabetic retinopathy or as an independent disease of the retina (Fung et al., 2022).

As mentioned above, diabetic retinopathy occurs due to microvascular damage to retinal capillaries. However, today there is abundant evidence that retinal (retinal) nerve dysfunction can occur long before the appearance of changes in the small blood vessels. Therefore, early diabetic retinopathy is considered not only as a vascular disease, but also as a neurovascular degenerative disease (Mavija, 2020). Current treatment focus on the late stages of diabetic retinopathy, when vision is already significantly affected. Therefore, prevention and timely detection of early changes is necessary in order to prevent and/or delay the onset of an advanced stage of the disease in which the patient has already significantly lost vision.

When serious complications of diabetes have already occurred in the eye, treatment is based on: retinal laser photocoagulation, micropulse laser treatment (for diabetic macular edema), intravitreal drug administration in the operating room called anti-VEGF (factors that prevent the growth of new blood vessels), and finally, vitrectomy.

Despite treatment, the fact remains that some patients continue to lose vision or do not see any improvement in vision after the resolution of macular edema due to retinal atrophy and/or ischemia (Simó et al., 2018).

Therefore, new and more effective preventive and interventional strategies are needed based on a better understanding of the pathogenesis of the early stages of the disease.

There are growing evidences clearly showing that neurodegeneration is an early event in the development of diabetic retinopathy that could be associated with the development of microvascular changes. Neurodegeneration has been shown to be present in the retina of diabetic patients even in the absence of clinically visible microvascular abnormalities. Therefore, neurodegeneration occurs

before microvascular disease, namely diabetic retinopathy (Simó et al., 2018; Khalaf et al., 2024).

Topical application of citicoline in the form of drops in combination with vitamin B12 has shown a protective effect on microvascular damage in diabetic retinopathy, as well as on the morphology of the retinal layers with stability of retinal function (Paravano et al., 2020). Tomić et al. (2025) shown a clinically positive effect of citicoline eye drops on hard exudates in DR.

Neuroprotection is considered a new treatment modality that can preserve retinal tissue, which further improves the outcome of treatment, especially in patients who are very “challenging” and incurable.

Age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is a disease of the macular area and is one of the most common causes of irreversible vision loss in people over 50 years of age. The main risk factor for the development of AMD is age over 50 years, followed by a positive family history, smoking, previous cataract surgery, atherosclerosis, obesity, arterial hypertension and cardiovascular disease, insufficient intake of vitamins A, C and E, omega 3 fatty acids, zinc and lutein in the diet and genetic factors (Čeklić and Mavija, 2015).

AMD is a multifactorial disease, in which the main factors for the development of the disease are changes in the structure and metabolism of a retina layer called the retinal pigment epithelium (RPE). The changes begin around the fourth decade of life and are more pronounced with increasing age (Hodžić et al., 2021).

Besides classic categorization on dry and wet macular degeneration, there are more detailed classifications. The classification of dry form of AMD relates to number and size of drusen and the changes in RPE. There is *early stage* with soft drusen, 64-124 µm in size and light pigment changes on the posterior pole, and *intermediate stage* with middle-sized drusen resulting in confluence and big drusen (> 125 µm) accumulated below retina. Late stage of AMD has two subtypes: *wet, exudative or neovascular* macular degeneration and *geographic atrophy* or dry degeneration (Hodžić et al., 2021). According to the literature, a dry form of AMD present in 10 - 20 % of patients progresses to wet form, where 40% of patients develop wet form of AMD on both eyes (Andrijević Derk, 2015).

If the wet form has developed (the late stage of the disease with neovascularization) the treatment choice is antiVEGF therapy, which inhibits vascular endothelial growth factor (VEGF) which is administered intravitreally. For patients with geographic atrophy (late-stage dry degeneration), an

adequate therapy has not yet been found, and irreversible vision loss in AMD is primarily attributed to retinal neurodegeneration and choroidal neovascularization that occur in the later stages of the disease (Lin et al., 2022).

Neuroprotection has emerged as a strategy to delay photoreceptor (RPE cell) death and preserve vision. One of advantages of neuroprotection is that it have the ability to slow RPE degeneration regardless of the underlying cause and may even generalize to other neurodegenerative retinal diseases. Citicoline has been shown to attenuate photoreceptor death (apoptosis) and as such represents a new potential modality for preserving vision in individuals with AMD (Lin et al., 2022; Nashine and Kenney, 2020).

Conclusion

Citicoline is an essential compound for the proper functioning of the brain in general and the visual system in particular. Although its potential in delaying and onset of certain retinal diseases has only recently been discovered, citicoline has already found its place as an adjuvant therapy in glaucoma and diabetic retinopathy among clinical ophthalmologists.

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