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Review

Nitric oxide-donating compounds for IOP lowering in glaucoma☆

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ABSTRACT

Introduction: An elevated intraocular pressure (IOP) remains the main risk factor for progression of glaucoma upon which we can efficiently act. Pharmacological strategies to reduce IOP are directed toward the reduction of aqueous humor (AH) production and/or the increase in AH drainage through the uveoscleral pathway. However, there are no drugs currently available as first-line treatment to increase AH outflow primarily *via* the conventional route. Ocular nitric oxide (NO) production takes place in AH outflow pathways and in the ciliary muscle, modulating the cellular response to elevated IOP.

Methods: This review describes the mechanism of action of endogenous NO and NO-donating compounds that are under research. It includes information regarding pre-clinical and clinical studies previously conducted with these compounds, discussing their role and therapeutic potential in the pharmacological treatment of ocular hypertension in glaucoma.

Results: The topical ocular administration of NO-donating compounds significantly lowered IOP and maintained it in animal models of glaucoma and subjects with ocular hypertension.

Conclusions: The mechanism of action of these compounds is novel and scientific evidence that shows promising results. However, there is a need for more comprehensive studies to assess long-term safety and tolerability in order to properly evaluate their use in chronic therapies.

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Donadores de óxido nítrico como hipotensores en glaucoma

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RESUMEN

Introducción: En relación con la progresión del glaucoma, la presión intraocular (PIO) elevada es el principal factor de riesgo sobre el que se puede actuar. Las estrategias farmacológicas destinadas a reducir la PIO tienen como objetivo la reducción de la producción de humor acuoso (HA) y/o el aumento de su drenaje a través de la vía uveoescleral. Sin embargo, en la actualidad no hay ninguna estrategia farmacológica de primera elección que de forma principal esté destinada a facilitar la salida de HA por la vía convencional. La producción de óxido nítrico (NO) a nivel ocular tiene lugar en las rutas de flujo de HA y en el músculo ciliar, modulando la respuesta celular en situaciones de PIO elevada.

Métodos: En esta revisión se describe el mecanismo de acción del NO endógeno así como de las nuevas moléculas donadoras de NO que se encuentran en fase de investigación. Además se incluye información acerca de los estudios preclínicos y clínicos realizados hasta la fecha con estos nuevos compuestos, discutiendo su potencial terapéutico en el tratamiento farmacológico de la hipertensión ocular en glaucoma.

Resultados: La administración de compuestos donadores de NO por vía tópica oftálmica proporciona un descenso de la PIO marcado y mantenido en modelos experimentales de glaucoma y en sujetos con hipertensión ocular.

Conclusiones: El mecanismo de acción de estos compuestos es novedoso y la evidencia científica muestra resultados prometedores. Sin embargo, para poder valorar su uso en terapias crónicas son necesarios más estudios que demuestren su seguridad y la eficacia a largo plazo.

Introduction

Glaucoma is the main worldwide cause of irreversible blindness.[1] It is estimated that 60.5 million people are affected by primary open angle glaucoma (POAG) and that this amount will increase up to 111.8 million in 2040.[2] Glaucoma is a progressive optic neuropathy in which high intraocular pressure (IOP) plays a crucial role. The course of the disease is chronic and the only treatment that has demonstrated to be effective to date is lowering IOP through pharmacological or surgical treatment. Glaucoma being a chronic and progressive pathology, it is usually necessary to increase the number of medicaments or consider additional surgery in order to maintain adequate intraocular pressure throughout the patient's life. The high frequency of glaucoma has turned it into a first order epidemiological problem due to the social and economic impact it entails and to the impairment in the quality of life of patients.

In the majority of cases, first line treatments are topical hypotensor medicaments.[3] Hypotensor agents exhibit 2 main mechanisms: diminishing aqueous humor (AH) (beta-blockers, carbonic anhydrase inhibitors, alfa-agonists) and increasing AH drainage through the uveoscleral pathway (prostaglandin analogs). It is known that changes produced in the anterior segment of the eye, specifically in the trabecular pathway (conventional), which accounts for up to 90% of AH drainage, are directly related to IOP variations occurring in glaucoma patients.[4] However, even though it has been demonstrated that some hypotensor agents exhibit secondary action through this pathway (adrenergic agonists), to date there is no medication available in clinic practice having the conventional pathway as main therapeutic target (trabecular mesh and/or Schlemm's canal).[5]

In part, the scientific focus in this multifactorial pathology aims at elucidating the physiopathological mechanisms that produce IOP increase and progressive loss of retinal ganglion cells (RGC) which gives rise to sectorial thinning of the retinal nerve fiber layer and visual field alteration. In this regard, the role of inflammatory mediators such as nitric oxide (NO) is being evaluated as a possible alternative for diminishing IOP and improving optic nerve head perfusion, which could slow down the progression of the disease.

This review describes the endogenous NO action mechanism as well as the new NO donating molecules under research (Fig. 1). It also includes information about pre-clinic and clinic studies conducted to date with these new compounds and discusses their therapeutic potential for the pharmacological treatment of glaucoma.

Nitric oxide as a cellular messenger

Nitric oxide or nitrogen monoxide (NO) is one of the smallest and most ubiquitous molecules. No nucleated cells have been described to date having the ability to synthesize NO,[6] which constitutes an important metabolite in mammal cells.[7]

NO is a colorless gas with neutral charge with a size not exceeding 30 Da. These physical characteristics allow its to diffuse through dialogical membranes at a very high speed