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MECHANISM OF OCULAR HYPOTENSIVE ACTION OF ANGIOTENSIN CONVERTING ENZYME INHIBITOR

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CONTENTS

ABSTRACT

Angiotensin converting enzyme inhibitors (ACEIs) have been shown to reduce intraocular pressure (IOP), however, their mechanism of IOP reduction is poorly understood. The possible mechanisms of ACEIs action are include stimulation of the prostaglandin (PG) synthesis leading to increased matrix metalloproteinase (MMP) and TNF-alpha activities, as well as reduction of angiotensin II type one receptor activity in the trabecular meshwork. The objective is to evaluate the mechanism of ocular hypotensive action of angiotensin converting enzyme inhibitors. In study one, the normotensive *Sprague Dawley* rats were divided into 4 groups (n=10). The group 1 and 4 were bilaterally pretreated with vehicle and then topically treated with single drop (10μL) of vehicle in the control eye and enalaprilat 1.00% (group 1) and losartan potassium 2.00% (group 4) in the contralateral eye. Groups 2 and 3 were bilaterally pretreated with TNF-alpha inhibitor (thalidomide 0.5%) and MMP inhibitor (GM-6001 0.05%) respectively, and subsequently were treated with single drop of vehicle in the control eye and enalaprilat in the test eye. IOP estimations were done using tonopen at baseline and subsequently at regular intervals. In study two 4 groups (n=5) of normotensive rats received bilateral topical treatment with vehicle (group 1), enalaprilat 1% (group 2), thalidomide 0.5% (group 3) and GM-6001 0.05% (group 4) for 7 days. Animals were sacrificed and total aqueous humor level of PG-$F_{2\alpha}$ was estimated using ELISA. In study one all groups showed significant IOP reduction in the test eye for first 6-8 hours post-treatment. However, enalaprilat treated group demonstrated significantly less IOP as compared to other groups. The maximum mean IOP reduction of enalaprilat treated group was 3.58±0.57 mmHg (20.3%) from the baseline. Thalidomide and GM-6001 pretreated groups showed maximum mean IOP reduction of 2.4±0.86 mmHg (13.4%) and 2.0±0.56 mmHg (11.2%), respectively. In losartan potassium treated group maximum mean IOP reduction was 2.35±1.39 mmHg (13.3%) from the baseline. In study two thalidomide and GM-6001 treated groups showed a trend towards decreased of PG-$F_{2\alpha}$ levels which was not observed in enalaprilat treated and control groups. The differences among groups were not significant. In conclusion, the potential mechanism of ACEI-induced ocular hypotension includes decreased angiotensin II type 1 receptor activation and increased MMP.

1.0 Introduction

Glaucoma is a heterogeneous group of diseases of ocular neuropathy characterized by slow progressive degeneration of the retinal ganglion cells (RGCs) and the optic nerve axons that eventually will lead to visual field deterioration (Agarwal, Gupta, Agarwal, Saxena & Agrawal, 2006). Globally, it accounts for about 66.8 million people who have suffer from visual impairment caused by glaucoma, implicated that glaucoma is the second most common cause of blindness worldwide. It is estimated that in 2010, there will be 60.5 million people with OAG and ACG and it is expected to increase to 79.6 million by 2020 (Gupta, D, Agrawal, Srivastava & Saxena, 2008). In general, there are usually no symptoms until the patient develops advanced visual field loss. Hence, it is extremely important for early detection and optimal management of glaucoma to preserve the vision and to reduce the economic consequences as glaucoma is a serious public health problem mainly in developing countries. It was demonstrated that undiagnosed glaucoma indirectly contributes to the raising mortality due to accidental causes. This is due to the finding of undiagnosed subjects older than 55 years old with primary open angle glaucoma (POAG) that has four-fold frequent to involve in car accidents (Izzotti, Bagnis & Saccà, 2006).

Glaucoma is believed to be multi-factorial in origin, with established genetic and biological risk factor (Goel, Picciani, Lee & Bhattacharya, 2010). High intraocular pressure (IOP) is well known as the most important risk factor for the development of glaucoma (Izzotti et al, 2006).

The secretion of aqueous humor and the regulations of its outflow are physiologically important for the normal function of the eye. The balance between aqueous humor production and its outflow is crucial for maintaining the normal IOP. Over production of aqueous humor or impaired in aqueous humor drainage beyond this range will cause elevated in IOP. On top of that, any increase in episcleral venous pressure will also increase the resistance to the aqueous humor outflow, thus increase in IOP (Murgatroyd & Bembridge, 2008).

Current therapeutic options for the management of glaucoma are focusing on prevention the risk factors with the primary aims to reduce the IOP to the desirable target as well as enhance the aqueous humor outflow.