OCULAR HYPOTENSIVE EFFECTS OF ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKERS IN RAT MODEL OF STEROID INDUCED OCULAR HYPERTENSION.

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OCTOBER 2013

ACKNOWLEDGEMENT

In the name of Allah the Most Merciful and the Most Gracious

All praise is to Allah, for its because of His countless blessings to me I was able to take up and finish my Advanced Medical Science course successfully. Thank you to the Faculty of Medicine, Universiti Teknologi MARA, the Dean, Prof. Dato' Khalid Yusoff and the program coordinator Prof Dr Nasimul Islam for offering me to join this program.

I would like to thank my supervisor Assoc. Prof. Dr. Renu Agarwal for her guidance and advices and much help to me since I first started to embark on this journey, and also to my co-supervisor Dr Anna Krasilnikova. I owe both of them so much, for without their assistance I wouldn't be able to complete my research. Also, I would like to thank Prof Kannankuthy and Dr Nor Salmah Bakar for lending their hands to help me during histopathological work. Not forgetting, Dr Norhafiza Razali, Laboratory Animal Care Unit staffs and Pathological Anatomy Laboratory staffs for their assistance and help. I would like to thank my colleagues and research mates for all the support and cooperation they have given me during the one-year course. I really appreciate all the things that each one mentioned here have done. Thank you all.

Last but not least, I would like to thank my family, for the endless support for me, from the beginning until the end of this journey.

Siti Nur Laili Mohamed, 2013

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ABSTRACT

Introduction: Glaucoma is associated with elevated intraocular pressure (IOP). As angiotensin II type 1 receptor blocker (ARB) has been shown to have oculohypotensive effect on rats with normal intraocular pressure, in this study we evaluated the IOP lowering effects of ARB in steroid-induced oculohypertensive rats. We also studied the effects of ARB on trabecular meshwork (TM) remodeling.

Methods: The elevation of IOP was achieved in rats by twice daily topical instillation of dexamethasone 0.1% over 36 days. Subsequently, IOP lowering effect of unilateral single drop application of losartan 2% were studied and compared with that of latanorpost. IOP lowering effect was also studied during twice daily instillation of losartan over 21 days. The changes in TM were studied after hematoxylin eosin staining. Aqueous humor MMP levels were estimated using ELISA.

Results: Unilateral single drop application of losartan potassium caused significant IOP reduction ($p<0.01$) starting at 1-hour and lasting for 11 hours post-instillation. The extent of IOP lowering was comparable to that of latanoprost, although, the duration of IOP lowering was shorter with losartan. Twice daily instillation of losartan over 21 days caused sustained IOP reduction as was the case with latanoprost. Histopathological examination showed significantly increased ECM deposition in steroid treated rats, which was significantly reduced after treatment with losartan as well as latanoprost. The mean aqueous humor MMP levels were significantly high in losartan and latanoprost treatment groups compared to vehicle treated group.

Conclusion: In conclusion, the angiotensin II type 1 receptor blocker, losartan potassium, when applied topically reduces IOP in rats with steroid-induced ocular hypertension. This reduction in IOP is attributed to increased MMP secretion and TM remodeling. The reduction in IOP is not associated with changes in systemic blood pressure and local adverse effects.

CHAPTER 1

INTRODUCTION

Glaucoma, an optic neuropathy, is characterized by progressive loss of retinal ganglion cells (RGCs), which leads to cupping of the optic disc and visual deficits. Glaucoma is often associated with increased intraocular pressure (IOP), and if left untreated, may lead to irreversible blindness. (Lee & McClusky, 2010). Epidemiological studies reveal that glaucoma affects approximately 70 million people worldwide (Quigley, 1996). By the year 2020, it is estimated that there will be 79.6 million people with primary open angle glaucoma (POAG) and angle closure glaucoma (ACG) and POAG will comprise of 74% of the figure, with 5.9 million people having bilateral blindness due to POAG. (Quigley & Broman, 2006). Glaucoma placed itself fifth in the ranking of ocular diseases contributing to blindness and in Malaysia, 1.8% of blindness is due to glaucoma. (Zainal, Ismail, Ropilah, Elias, Arumugam, Alias, Fathilah, Lim, Ding, Goh, 2002).

The only known modifiable risk factor for the development and progression of this disease is elevated IOP. (Lee & McClusky, 2010). Under normal conditions, IOP is regulated by a balance in the rate of aqueous humor secretion by the ciliary body and its drainage via trabecular and uveoscleral pathways. (Goel, Picciani, Lee, Bhattacharya, 2010). If this balance is disrupted, i.e. the aqueous humor is overproduced or there is some blockade in the outflow, ocular hypertension develops. As elevated IOP is the only modifiable risk factor, it has become the most important aspect to be tackled in glaucoma treatment. Most of the currently available antiglaucoma drugs act by lowering IOP. However, most of them do not provide adequate control of IOP and cause many side effects, which necessitates the search for a newer drugs that can be both IOP-stabilizing and cause no or least adverse effect.

Oral administration of the angiotensin II type 1 receptor blocker (ARB), losartan, has been shown to reduce IOP in human subjects, both with normal tension glaucoma and POAG, by significantly