RETINAL GANGLION CELL PROTECTION AGAINST ENDOTHELIN-1-INDUCED INJURY BY MAGNESIUM ACETYL TAURINATE IN RATS

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Dear Sir/Madam

ETHICS APPROVAL BY UiTM CARE : UiTM Care : 124/2015

Title Research : Retinal Ganglion Cell Protection Against Endothelin-Induced Injury By Magnesium Acetyl Taurinate In Rats.

The following members attended the above meeting:

Name	Designation
Prof. Dr.Aishah Adam	Professor and Dean Faculty of Pharmacy
Prof Dr Harbindar Jeet Singh	Lecturer Faculty of Medicine,UiTM Campus Sg Buloh
Associate Prof Dr Vellayan a/l Subramaniam	Lecturer and Coordinator Laboratory Animal Facility and Management (LAFAM) Faculty of Pharmacy
Associate Prof Dr Kazi Ahsan Jamil	Lecturer Faculty of Dentistry,UiTM
Associate Prof Dr Zaini Mohd Zain	Lecturer Faculty of Medicine,UiTM Campus Sg Buloh
Dr Mizaton Hazizul Hassan	Lecturer, Faculty of Pharmacy

The Research Committee on the Ethical Use of Animals has evaluated the research proposal entitled above on the 06th November 2015. This committee has agreed to fully endorse and recommend that the research be allowed to start without any amendments.

Thank you

Yours truly

PROF DR AISHAH ADAM
Chairman
Research Committee on the Ethical Use in Research (UiTM Care)
Universiti Teknologi MARA

cc: Asst Vice Chancellor (Research)
Research Management Institut

ABSTRACT

Glaucoma, the leading cause of irreversible blindness, is characterized by apoptotic death of retinal ganglion cells (RGCs). Elevated levels of endothelin1 (ET1), a potent vasoconstrictor, have been detected in the eyes and plasma of glaucoma patients. Increased endothelin 1 causes retinal ischemia increased expression of nitric oxide synthase (NOS) isoforms and oxidative stress, which culminate into RGC apoptosis. Considering the vasodilating, and antioxidant properties of magnesium acetyltaurinate (MgAT) we hypothesized that it can prevent endothelin 1-induced vasospasm, improve retinal perfusion and reduce retinal oxidative stress by altering expression of 3 isoforms of NOS. Rats received single intravitreal injection of vehicle/ET1/ET1 with MgAT. Subsequently, histopathological examination of optic nerve were done to detect the extent of optic nerve damage. Immunochemical detection of NOS isoforms and estimation of NO and antioxidants was done in retina. It was observed that MgAT reduces retinal and optic nerve damage. This neuroprotective effect of MgAT was associated with reduced expression of NOS1 and 2, increased expression of NOS3 and reduced retinal oxidative stress. The results of this study were published in a Q1 journal and were presented in 2 national and 3 international conferences. One student has completed her Master's research work and has been promoted to PhD.

Further studies are needed to explore the full potential of MgAT as antiglaucoma agent and to develop its formulation.

INTRODUCTION

Glaucoma, an optic neuropathy, results from retinal ganglion cells (RGC) death and leads to progressive vision loss (Weinreb and Khaw 2004; Vecino and C. Sharma 2011). Population based studies have shown that one in 40 adults older than 40 years has glaucoma with vision loss, which equates to 60 million people worldwide. It is estimated that 8·4 million people worldwide have blindness due to glaucoma (Quigley 2011). Although elevation of IOP remains an important risk factor for glaucoma, not all glaucoma cases are associated with this risk factor. Approximately one third of all glaucoma cases have normal IOP, often within a range of 15 and 20 mmHg, and this is known as normal tension glaucoma (NTG) (Buckley et al. 2002; R. Anderson 2011). Despite absence of significantly elevated IOP in all glaucoma cases, reduction of IOP remains the only treatment for glaucoma. There is adequate evidence to suggest that generalized vascular defect which produce alterations in both the ocular and systemic circulations such as decreased velocity of blood flow and increased resistance in retinal vessels are present in glaucoma (Ko et al. 2000; Buckley et al. 2002). Vascular dysregulation involving alterations in retinal perfusion are associated with ischemia-reperfusion induced damage. Furthermore, retinal ischemia induces oxidative stress and finally RGC apoptosis (Flamer J. et al. 2002).

Recent evidence showed the association of glaucoma with elevated level of plasma endothelin-1 (ET1). ET1 and Nitric Oxide (NO) regulate vascular tone locally. ET1 is a family of small potent vasoactive peptides. Due to its vasoconstrictive properties, it causes retinal ischemia; and has been recognized as an important target for the treatment of glaucomatous neuropathies. Both ET1 and NO are synthesized and released from ciliary process in the eye into the aqueous humor (Choritz et al. 2012). They are also produced by other cells involved in vascular diseases such as leukocytes, macrophages and smooth muscle cells (Luscher and Barton 2000). Excess of ET1 reduces optic nerve blood flow and promotes RGC death and decreased axon survival rates. ET1-induced RGC death also occurs due to reduced availability of growth factors caused by alterations in axonal transport (J. Lau et al. 2005). NO is a vasodilator and is believed to contribute to regulation of retinal perfusion and redox status (Dai et al. 2011). Its excessive production, however, increases nitrosative stress and is associated with altered expression of 3 isoforms of nitric oxide synthase (NOS).

Magnesium has previously been shown to improve visual field in NTG patients (Korkmaz et al. 2013). It is a physiological calcium blocker and can counteract the effects of ET1 by decreasing the vascular tone and increasing the retinal blood flow. This may involves altered expression of NOS and reduced retinal oxidative and nitrosative stress. Taurine is the most abundant amino acid in the ocular tissue and is a potent antioxidant. Hence, considering the vasodilating and antioxidant properties of magnesium acetyltaurinate, we hypothesized that it can prevent ET1-induced loss of RGCs by reducing the retinal oxidative stress and altering the expression of 3 isoforms of NOS.