

The role of trimetazidine in the protection of the retina

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Abstract

Tissue ischaemia is an important factor in the development of several eye diseases. The commonly accepted idea regarding management of ischaemic effects is that a normal blood flow should be increased. Trimetazidine, an anti-ischaemic agent, can have a positive effect on retinal disorders with an ischaemic component. Trimetazidine seems to have an influence on selected visual parameters (improves visual acuity and contrast sensitivity) as an additional therapy in treatment of patients with primary open angle glaucoma and degenerative myopia. A positive effect on other retinal disorders with an ischaemic component, e.g. diabetic retinopathy, age-related macular degeneration (AMD) or inflammatory diseases, requires further investigations.

Key words: trimetazidine, retinal ischaemic diseases, neurodegeneration, neuroprotection.

Trimetazidine (TMZ) is an anti-ischaemic agent which is frequently used as a prophylactic treatment of episodes of angina pectoris and as a symptomatic treatment of vertigo and tinnitus [1]. It has also shown beneficial effects in models of visual dysfunction, but the mechanism(s) by which this occurs is yet undefined. Trimetazidine is a derivative of piperazine and selectively inhibits beta-oxidation of fatty acids. It leads to inhibition of the oxidation of free fatty acids and secondarily increases glucose oxidation.

Trimetazidine usefully modifies the metabolism of energetic compounds and has anti-ischaemic characteristics, acting on the cellular level. It was proved in cardiology that pre-procedural acute oral TMZ administration significantly reduces PCI (percutaneous coronary intervention) -induced myocardial infarction so this may indicate a positive role of trimetazidine in other ischaemic diseases, for example in microvascular abnormalities of the choroid and the retina. Trimetazidine seems to have an influence on selected visual parameters (improves visual acuity and contrast sensitivity) as an additional therapy in treatment of patients with primary open angle glaucoma and degenerative myopia [2]. It is possible that trimetazidine may have a positive effect on other retinal disorders with an ischaemic component, e.g. in diabetic retinopathy, age-related macular degeneration (AMD) or in inflammatory diseases. Mohand-Said et al. indicated that treatment with intraperitoneal injection of trimetazidine shows significant protection against retinal ischaemic damage induced by ischaemia-reperfusion, followed by an increase in intraocular pressure (IOP) to 160 mmHg for 60 min, in a rat model [3]. Chronic ocular hypertension in rats produces dramatic damage to all retinal layers and the optic nerve observed by morphological and functional

methods which significantly correlate with the IOP elevation [4]. The outer retina of glaucomatous rats seems to be more susceptible to the damage due to chronic elevation of the IOP. Chronic hypertensive rat eyes have the capacity to temporarily recover function of the inner retina and optic nerve. Trimetazidine protects the rat retina from pressure-induced ischaemic injury and might be considered a potential therapeutic modality for combating retinal ischaemia [5]. Deprivation of both glucose and oxygen for 60 min at 30°C produces severe acute neurodegeneration [6]. Ischaemic neurodegeneration contributes to many retinal diseases and is characterized by bull's eye formation in the inner nuclear layer and spongy appearance in the inner plexiform layer. Baltalarli et al. demonstrated the neuroprotective effect of trimetazidine on ischaemic-reperfusion injury tested by a randomized, controlled, prospective study in a rat model of transient global cerebral ischaemia. The results suggest that trimetazidine reduces cerebral injury and preserves neurological function in transient global ischaemia in rats caused by the occlusion of carotid arteries. It is suggested that the beneficial effects of trimetazidine can be explained by an optimization of energy metabolism. Trimetazidine acts by inhibition of fatty acid oxidation, secondary to inhibition of long chain 3-ketoacyl CoA thiolase. This results in an increase in glucose oxidation, resulting in improved coupling between glycolysis and glucose oxidation.

If even low concentrations of glucose were delivered to an ischaemic retina in vitro, substantial neuroprotection could be achieved. This may have implications for the management of acute retinal ischaemic episodes. These results suggest that retinal excitotoxic damage in vivo can occur secondarily to depletion of cellular energy reserves, and therefore may be prevented by simple procedures that maintain the availability of energy sources.

Local vascular disturbances may likewise be risk factors in glaucoma. The association between vasospastic disorders like Reynaud's syndrome and migraine and glaucoma has led to the assumption that vascular endothelial dysfunction, causing abnormal contractility of the blood vessels, is one of the many factors involved in the pathogenesis of glaucoma. The blood flow in the region of the optic nerve head is reduced mainly in patients suffering from normal-tension glaucoma. Vascular impairment at the level of the optic nerve head in primary open angle glaucoma inhibits axoplasmic flow and leads to retinal ganglion cell apoptosis [7-9]. It is postulated to be an important factor in the development of glaucoma, besides elevated intraocular pressure. Clinical studies have provided evidence that appropriate blood flow in the posterior segment of the eye appears to be an absolute prerequisite for

maintaining the function of the optic nerve [10]. Administration of drugs enhancing optical nerve perfusion plays an important role in glaucoma treatment, especially in low tension glaucoma. Recently, attention has been paid to the use of neuroprotective drugs administered systemically in the treatment of primary open angle glaucoma. Improvement in contrast sensitivity and visual acuity in patients with primary open angle glaucoma and degenerative myopia after trimetazidine therapy was observed. Trimetazidine due to its cytoprotective is beneficial for neurosensory cells of the retina and the optic nerve in ischaemic conditions.

Tissue ischaemia is an important factor in the development of several eye diseases. Ischaemia causes tissue hypoxia, affects cellular metabolism, and impairs functioning of the cells. This can contribute to irreversible tissue injury including the neurosensory retina and optic nerve. The commonly accepted idea regarding management of ischaemic effects is that a normal blood flow has to be increased or restored. Trimetazidine administered prophylactically prevents injury of the retinal cells in ischaemia induced by intraocular pressure increase and blood flow disorders.

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