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## **High glucose and hypoxia-induced damage in the inner blood retinal barrier is counteracted by thiamine supplementation**

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**Design of study:** Although diabetic retinopathy (DR) has long been considered a microcirculatory disease, recent evidence shows that retinal neurodegeneration may occur early in its pathogenesis. New treatments targeting both vascular and neuronal damage are therefore needed. Endothelial cells, pericytes and Müller cells are three important components of the inner blood-retinal barrier (iBRB), playing a key-role during the development of DR. Müller cells may act as a link between microvascular damage and neurodegeneration. High glucose-induced metabolic damage in microvascular cells in vitro and progression of retinopathy in diabetic animals is prevented by thiamine. Diabetic subjects often show decreased levels of thiamine.

**Purpose:** This study was aimed at verifying if thiamine protects the iBRB from stress and apoptosis induced by diabetic-like conditions, and examine the molecular mechanisms involved in preventing damage.

**Methods:** Human Microvascular Endothelial cells (HMEC), retinal pericytes (HRP), and Müller cells (MIO-M1) were exposed to hyperglycaemic-like conditions (intermittent high glucose, intHG, and/or hypoxia), with/without thiamine over-supplementation. The expression of the adhesion molecules CD29,  $\alpha$ V $\beta$ 3 and ICAM-1 were investigated by FACS, metalloproteases MMP-2, MMP-9, and their inhibitor TIMP-1 by Western blotting, and the synthesis and secretion of angiogenic factors (VEGF, Ang1, Ang2, HIF-1 $\alpha$ ) by ELISA and Western blotting.

**Results:** MMP2 and MMP9 expression was increased by intHG and normalized by thiamine in all cell types, while TIMP-1 increased in HRP only. Diabetic like-conditions enhanced the expression of Ang2, VEGF and HIF-1 $\alpha$  in HMEC, which was again counteracted by thiamine. As regards adhesion molecules, CD29 was increased in HRP by intHG and ICAM-1 in HMEC by intHG+hypoxia; again thiamine was able to neutralize these effects.

**Conclusions:** Diabetic-like conditions impair the expression of angiogenic molecules in cells of the iBRB. Endothelial cells and pericytes seem to be the primary targets. Thiamine supplementation is able to counteract the damage induced by high glucose and hypoxia. Therefore, thiamine could be further investigated as a putative therapeutic approach for DR.