MODULATION OF DIABETIC RETINOPATHY BY MELANOCORTIN MC1 AND MC5 RECEPTOR SUBTYPES ACTIVATION IN A MOUSE MODEL OF STZ-INDUCED DIABETIC RETINOPATHY AND RETINAL CELLS CULTURE

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Diabetic Retinopathy (DR) is the vascular and neural injury of the retina caused by metabolic disorders in diabetes. In the retinal vascular endothelial cells a protective effect can be exerted by α - melanocyte stimulating hormone (α-MSH), a modulator of immune-response that binds to 5 subtypes of G protein–coupled melanocortin receptors (MC1R-MC5R). A model of streptozotocin-induced diabetic retinopathy (DR) in mice was used in order to characterize the melanocortin receptor subtypes involved in this protection. Intravitreal injections of melanocortin receptor agonists/antagonists, fluorescein angiography (FAG), RT-PCR, western blotting, immunohistochemistry, and ELISA were performed. 12 weeks after the induction of diabetes. FAG showed microvascular changes typical of DR in 80% of the mice. These microvascular changes were also evident after 16 weeks of diabetes. Interestingly, intravitreal injections of the MC5 agonist PG-901 at 7.32 ± 2.28 nM showed a significant retina protection, with no alterations in size, shape and/or course of the retina vessels (Rossi et al., 2016). In contrast, intravitreal injection of the MC5 melanocortin receptor antagonist PG20N at 130 nM (Grieco et al., 2008) worsened the signs of DR captured by FAG. In addition to this structural data we further aimed at investigating the functionality and integrity of retinal photoreceptors. For this reason, we investigated in primary cell cultures isolated from retinas of C57BL/6 mice, the hypothesis where the photoreceptors integrity would be preserved by MC5 receptor agonist PG-901 in condition of high levels of glucose (25 mM) that simulate the same pathological conditions of diabetic retinopathy (Baptista et al., 2015). The cells were first characterized through labeling with rhodopsin (opsin) and recovering, that show the presence of the photoreceptors in retinal cells. The results claim for high staining of these two markers in the cells treated with the MC5 agonist PG-901 with respect to the cells without treatment, and thus with high glucose only. Moreover, considering that photoreceptor membranes are particularly rich in polyunsaturated fatty acids and extremely vulnerable to the oxidative damage induced by free radicals (Varano M, 2007), we observed that an agonism at MC5 receptors promotes increased levels of GPx and MnSOD from retinal cells. In conclusion, the activation of the melanocortin MC5 receptor subtype reduces the retinal damage in a mouse model of STZ-induced retinopathy and in a high glucose-cultured retinal cells it preserves photoreceptors.

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