Predominant activation of MC1 and MC5 melanocortin receptor subtypes reduces the retinal damage in a mouse model of STZ-induced diabetic retinopathy

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Diabetic Retinopathy (DR) is the vascular and neural injury of the retina caused by metabolic disorders in diabetes. Recently Zhang et al., (2014) showed that in the retinal vascular endothelial cells a protective effect can be excerted 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 study the possible involvement of melanocortins in the genesis of DR and to characterize the melanocortin receptor subtypes involved in it. 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 evidents after 16 weeks of diabetes, and interestingly there were no signs of vascular leakage. Occludin, a sensible marker of cell tight junctions, appears to be progressively decreased in the eye of mice developing retinopathy. RT-PCR showed that the most abundant receptors expressed in the retina were the MC1 and MC5. Therefore, intravitreal injections of MCRs selective agonists and antagonists were performed once a month in a volume of 5μL of saline in order to activate/deactivate these receptors. The selective MC_1receptor agonist BMS-470539 at dose of 18.47 $mg \cdot kg^{-1}$(corresponding to 33 $\mu mol \cdot kg^{-1}$, Leoni et al., 2010) and the MC5 agonist PG-901 at 7.32±2.28nM (Moller et al., 2011) showed a significant retina protection, with regular course and caliber of retinal vessels without microvascular changes compared to the untreated retinopatic rats, as evidenced by FAG 12 weeks after induction of diabetes. No evidence of retinal vessels leakage was seen after 12 weeks and even after 16 weeks of diabetes. We also found no alterations in size, shape and/or course of the vessels. 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. Macrophage M1, inflammatory cytokines IL-1α, IL-1β, IL-6, chemokines MIP-1α, MIP-2α, MIP-3α and the markers of vessel proliferation VEGF and Ki-67 were abundantly increased during the development of retinopathy and further exacerbated by the MC5 antagonist PG20N. The MC1 agonist BMS-470539 and the MC5 agonist PG-901 restored the normal pattern of these mediators within the retina. Therefore, in conclusion, the predominant activation of the melanocortin MC1 and MC5 receptor subtypes reduces the retinal damage in a mouse model of STZ-induced retinopathy.

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