Inhibition of ocular Aldose Reductase by a new benzofuroxane derivative (BF-5m) ameliorates rat endotoxic uveitis

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Uveitis is an inflammation of the uveal tract including the iris, ciliary body and choroid, characterized by elevated levels of proinflammatory cytokines and reactive oxygen species (ROS) in ocular tissue (Hattori et al. 2010). Recent evidents show that the inhibition of aldose reductase (AR), a key enzyme of the polyol pathway able to convert the excess glucose into sorbitol with the consequent formation of ROS, prevents or decreases the lipopolysaccharide- (LPS-) induced uveitis in rats, the experimental animal model closest to human uveitis (Yadav et al. 2007, 2011). In line with this evidence, the present study investigated the effects of a new aldose reductase (AR) inhibitor benzofuroxane derivative 5(6)-(benzo[*d*]thiazol-2-ylmethoxy) benzofuroxane (BF-5m) (Sartini et al. 2012) on the biochemical and tissue alterations induced by LPS- induced uveitis in rats. BF-5m has been administered intravitreally, in order to assess the expression and levels of: (i) inflammatory markers such as the ocular ubiquitin-proteasome system, NF-κB, TNF-α, and MCP-1; (ii) prooxidant and antioxidant markers such as nitrotyrosine, manganese superoxide dismutase (MnSOD), and glutathione peroxidase (GPX); (iii) apoptotic/antiapoptotic factors caspases and Bcl-xl; (iv) markers of endothelial progenitor cells (EPCs) recruitment such as CD34 and CD117. 5 μL of BF-5m (0.01; 0.05; and 0.1 μM) into the right eye decreased in a dose-dependent manner the LPS-induced inflammation of the eye, reporting a clinical score 1. BF-5m reduced the ocular levels of ubiquitin, 20S and 26S proteasome subunits, NF-κB subunits, TNF-α, MCP-1, and nitrotyrosine. BF-5m ameliorated LPS-induced decrease in levels of MnSOD and GPX. Antiapoptotic effects were seen from BF-5m by monitoring the expression of Bcl-xl, an antiapoptotic protein. Similarly, BF-5m increased recruitment of the EPCs within the eye, as evidenced by CD34 and CD117 antibodies.

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