World Academy of Science, Engineering and Technology
International Journal of Health and Medical Engineering
Vol:11, No:09, 2017

Effects of Valproate on Vascular Endothelial Growth Factor in the Retina Associated with Choroidal Neovascularization

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Abstract : Valproate (VPA) is commonly used in the treatment of bipolar disorder and epilepsy. The mechanism is complicated, including its ability to inhibit histone deacetylases (HDACs). Here, we show that VPA attenuated VEGF gene expression and the morphological changes in choroidal neovascularization (CNV) induced by photocoagulation in retina. C57BL/6 mice were injected subcutaneously at 300mg/kg twice daily with VPA before insult. Vascular endothelial growth factor (VEGF)-A and VEGF-B were examined in the eyes of VPA-treated mice and in human retinal pigment epithelial cell lines (ARPE-19) exposed to VPA. In addition, CNV was induced by photocoagulation in mice injected with VPA, and the volume of CNV was compared by fluorescence-labeled choroidal flat mount. Morphological changes were analyzed on stained histological sections. Western blot analysis was used to determine protein levels of VEGF-A and VEGF-B, and acetylation of histone H3 in each group. VPA injected intraperitoneally attenuated the VEGF-A and VEGF-B expression in the retina, accompanied by the hyperacetylation of retina tissue, indicating that VPA acts directly on retina tissues through acetylation to reduce the expression of VEGF. VPA also attenuated the VEGF-A mRNA expression in the retinal pigment epithelium showed by immunohistochemistry. Moreover, the administration of VPA significantly attenuated photocoagulation-induced CNV in mice. These results demonstrate that VPA attenuated VEGF production in retina associated with choroidal neovascularization possibly via the HDAC inhibition.

Keywords : retina, acetylation, chorodial neovascularization, vascular endothelial growth factor
Conference Title : ICCEO 2017 : International Conference on Clinical and Experimental Ophthalmology
Conference Location : London, United Kingdom
Conference Dates : September 21-22, 2017