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Modulating Blood-Retinal Barrier: The Power of Ginsenosides

Yong-Sun Maeng, Jeong Hun Kim, Young-Myeong Kim, Young-Joon Surh, Young Suk Yu, Jeong Hill Park, Young-Guen Kwon.

From the Department of Biochemistry (Y.S.M., Y.G.K.), College of Sciences, Yonsei University, Seoul; and Department of Ophthalmology (J.H.K., Y.S.Y.), Seoul National University College of Medicine; Department of Molecular and Cellular Biochemistry (Y.M.K.), School of Medicine, Kangwon National University, Chunchon, Kangwon-Do; and Research Institute of Pharmaceutical Sciences (Y.J.S, J.H.P), College of pharmacy, Seoul National University, Seoul, Republic of Korea.

Tissues of the central nervous system, including the brain and retina, depend on intact blood-brain barrier (BBB) and blood-retinal barrier (BRB), respectively, to separate them from the peripheral circulation. These barriers share anatomical and physiological properties and play a pivotal role in protecting the neural tissue from exogenous toxins, buffering variations in blood composition and preventing free diffusion of solutes and haematogenous cells in the brain and retina. Disruption of the barriers occurs in a number of pathological conditions. In particular, breakdown of the inner BRB is a major cause of visual loss in a number of human ocular disorders including diabetic retinopathy (DR), sickle-cell disease, and cystoid macular edema. The mechanical barrier is primarily attributed to the presence of tight junctional intercellular complexes between the endothelial cells of the retinal vasculature. Tight junctions (TJs) make a seal around the circumference of cells and consist of a number of protein components, including the claudin family, occludin, and zonula occludins-1, -2, and -3 (ZO-1, ZO-2 and ZO-3), which interact with claudins and occludin. Claudin-1 and occludin have multiple transmembrane domains and form homodimeric bridges with adjacent cells, creating a physical blockade to paracellular diffusion. ZO proteins stabilize the TJ complex by linking occludin and claudins to the actin cytoskeleton.

DR is a common complication of diabetes and a leading cause of legal blindness in working-age adults. One of the earliest clinically detectable signs of DR is increased vascular permeability, due to a breakdown in the BRB, which causes macular edema. This is followed later by the development of vascular microaneurysms, deposition of lipoprotein exudates called drusen, and finally vascular proliferation. In current research on the pathogenesis of diabetic retinopathy, a great deal of effort has been focused on vascular endothelial growth factor (VEGF) because it is elevated in DR and causes increased permeability by altering tight junction integrity at the plasma membrane. Although the molecular mechanism by which VEGF stimulates tight junction disassembly and permeability in vascular endothelial cells have not been completely elucidated, recent studies have demonstrated the critical involvement of signaling pathways

downstream of VEGFR2 that leads to phosphorylation of occludin and ZO-1. In addition, such phosphorylation leads to its internalization by endocytosis and internalized occludin may be directed to a degradation pathway. Thus, understanding and prevention of VEGF-induced TJ disassembly and permeability is potentially important and could present therapeutic targets to prevent vascular pathobiology.

In the present study, we have evaluated the pharmacological effects and underlying molecular mechanisms of various ginsenosides isolated from the Korean ginseng and its processed form (sun ginseng) on vascular pathophysiology. Among ginsenosides tested in this study, Rg3(S), Rg5, and RK1 effectively inhibited serum deprivation-induced apoptosis of retinal endothelial cells. RK1 showed the most profound effect with half maximal inhibition at 5 ug/ml. We further investigated the effect of RK1 on VEGF-induced endothelial permeability. Treatment of retinal endothelial cells with VEGF significantly increased permeability and decreased the TJ proteins such as occludin, ZO-1, and ZO-2 at cell-cell junctions. These changes were markedly reversed by pretreatment of RK1. To confirm the effect of RK1 on VEGF-induced vascular leakage in vivo, VEGF was injected into the vitreous cavity of mouse eye, resulting in a marked retinal vascular leakage as evidenced by widespread, diffuse fluorescence. By contrast, the retinal vessels of the mice co-administrated with RK-1 remained clearly delineated with little or no leakage. Consistently, VEGF reduced TJ proteins in mouse retinal vessel endothelium and this effect was blocked by co-treatment of RK-1. Most importantly, diabetic mice induced with streptozotocin showed increased retinal vascular leakage with significant reduction in TJ proteins and this pathology was prominently ameliorated by treatment with RK-1. These findings suggest that a subgroup of ginsenosides including RK-1 possesses the chemical scaffold as a novel prototype compound for preventing the pathogenesis of diabetic retinopathy.