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혈관내피세포 보호에 의한 fenofibrate의 당뇨병성 신경증 개선 효과

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정성진, 임지희, 김민영, 김태우, 신석준, 최범순, 김형욱, 김용수, 장윤식, 박철휘

Fenofibrate Ameliorates Diabetic Peripheral Neuropathy via Promoting Endothelial Cell Survival in db/db Mice

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Introduction: Peroxisome proliferator-activated receptor (PPAR)α activation stimulates angiogenesis and maintains endothelial function through a vascular endothelial growth factor (VEGF)-dependent mechanism in type 2 diabetes. We hypothesized that fenofibrate might have therapeutic potential for preventing endothelial cell damage in diabetic peripheral neuropathy (DPN). Roles of VEGF and fenofibrate in DPN were examined in db/db mice that had VEGF receptor (VEGFR)-1 and VEGFR-2 inhibition using selective anti-flt1 hexamer and anti-flk1 heptamer together.

Methods: Male db/db mice and db/m mice at 8 wks of age with VEGFR inhibition, using selective anti-flt1 hexamer and anti-flk1 heptamer together, were treated with or without fenofibrate for 12 weeks.

Results: The db/db mice with VEGFR inhibition developed more severe nerve injury than db/db mice as evidenced by an increase in tactile threshold and a delay in motor nerve conduction. In db/db mice with VEGFR inhibition, the nerve fibrosis (TGFβ1 expression), neural ischemia (HIF-1α expression) and oxidative stress (8-OHdG) related to the vascular rarefaction (PECAM-1 expression) were more prominent compared to the control db/db mice, suggesting more severe ischemic injury, which were associated with an increase in number of apoptotic cells in the sciatic nerve. More severe derangement of the myelin with axonal shrinkage, a decrease in unmyelinated fibers, and endothelial cell damage in the sciatic nerve were noted in the db/db mice with VEGFR inhibition using an electron microscopy. In the cultured HUVECs, a high-glucose media with VEGFR inhibition induced more apoptotic cell death compared to a high-glucose media without VEGFR inhibition. The significant decrease in the PI3K-Akt-eNOS pathway was noted in a high-glucose media with VEGFR inhibition. Of great interest, fenofibrate reversed the development of DPN in the db/db mice with VEGFR inhibition and endothelial dysfunction of HUVECs in a high-glucose media with VEGFR inhibition by the activation of PI3K-Akt-eNOS pathway, suggesting that in a high-glucose state VEGFR inhibition could give more endothelial damage and preservation of endothelial function could be provided, at least in part, by fenofibrate.

Conclusion: These results demonstrated that PPARα activation could ameliorate DPN aggravated by VEGFR inhibition in type 2 diabetes. Fenofibrate may have a novel property that can control endothelial cell damage found in the DPN.

Key Words: 당뇨병성 말초신경병증, 혈관내피세포, fenofibrate
Diabetic peripheral nephropathy, Endothelial cell, PPARα