Vitamin D and rosuvastatin obliterate peripheral neuropathy in a type-2 diabetes model through modulating Notch1, Wnt-10Ŭ, TGF-ɓ and NRF-1 crosstalk

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Abstract

Aims: Vitamin D and rosuvastatin are well-known drugs that mediate beneficial effects in treating type-2 diabetes (T2D) complications; however, their anti-neuropathic potential is debatable. Hence, our study investigates their neurotherapeutic potential and the possible underlying mechanisms using a T2D-associated neuropathy rat model.
Main methods: Diabetic peripheral neuropathy (DPN) was induced with 8 weeks of administration of a high fat fructose diet followed by a single i.p. injection of streptozotocin (35 mg/kg). Six weeks later, DPN developed and rats were divided into five groups; viz., control, untreated DPN, DPN treated with vitamin D (cholecalciferol, 3500 IU/kg/week), DPN treated with rosuvastatin (10 mg/kg/day), or DPN treated with combination vitamin D and rosuvastatin. We determined their anti-neuropathic effects on small nerves (tail flick test); large nerves (electrophysiological and histological examination); neuronal inflammation (TNF-Ŭ and IL-18); apoptosis (caspase-3 activity and Bcl-2); mitochondrial function (NRF-1, TFAM, mtDNA, and ATP); and NICD1, Wnt-10Ŭ/ɓ-catenin, and TGF-ɓ/Smad-7 pathways.
Key findings: Two-month treatment with vitamin D and/or rosuvastatin regenerated neuronal function and architecture and abated neuronal inflammation and apoptosis. This was verified by the inhibition of the neuronal content of TNF-Ŭ, IL-18, and caspase-3 activity, while augmenting Bcl-2 content in the sciatic nerve. These treatments inhibited the protein expressions of NICD1, Wnt-10Ŭ, ɓ-catenin, and TGF-ɓ; increased the sciatic nerve content of Smad-7; and enhanced mitochondrial biogenesis and function.
Significance: Vitamin D and/or rosuvastatin alleviated diabetes-induced neuropathy by suppressing Notch1 and Wnt-10Ŭ/ɓ-catenin; modulating TGF-ɓ/Smad-7 signaling pathways; and enhancing mitochondrial function, which lessened neuronal degeneration, demyelination, and fibrosis.

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