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CEBPβ regulation of endogenous IGF-1 in adult sensory neurons can be mobilized to overcome diabetes-induced deficits in bioenergetics and axonal outgrowth

Aim: To determine the role and regulation of insulin-like growth factor 1 (IGF-1) signalling in the pathogenesis of diabetic neuropathy.
Methods: The authors examined IGF-1 levels and cellular localization in rodent models of type 1 and type 2 diabetes as well as prediabetic high-fat fed mice using single-cell RNA sequencing (scRNA-Seq) and in situ hybridization analyses. The effect of IGF-1 on neurite outgrowth and bioenergetics was further investigated in complimentary *in vitro* experiments using cultured sensory neurons exposed to hyperglycaemic conditions with or without IGF-1 overexpression or inhibition. Moreover, chromatin immunoprecipitation (ChIP) and luciferase-reporter assays identified how IGF-1 gene promoter is regulated at the transcription level.
Results: The authors demonstrated that diabetes, particularly hyperglycaemia suppresses IGF-1 levels in dorsal root ganglia (DRG), an effect which is partly mediated by the polyol pathway, a known pathomechanism in diabetic neuropathy. They also uncovered a key role for IGF-1 in the regulation of mitochondrial bioenergetics and neurite outgrowth in sensory DRG neurons. Indeed, IGF-1 inhibition reduced neurite outgrowth and mitochondrial respiration in cultured DRG neurons from diabetic rats. They further identified CEBPβ as an important regulator of IGF-1 transcription, which is reduced under diabetic conditions. Lastly, their data showed that CEBPβ overexpression enhances mitochondrial respiration and axonal regeneration via IGF-1 upregulation.
Conclusions: Taken together, this study suggests that IGF-1 is a critical neurotrophic factor required for sensory neuron mitochondrial function and axonal outgrowth. Under diabetic conditions, hyperglycemia reduces IGF-1 production and secretion in DRG neurons, which in turn compromises bioenergetics and axonal regeneration, and is likely to contribute to diabetic neuropathy pathogenesis.

Comments. Diabetic neuropathy is a disabling complication with limited treatment options, partly due to our incomplete understanding of disease pathogenesis. Thus, the quest for novel therapeutic approaches is urgent. IGF-1 is critical for neuronal cell maintenance, metabolism, and survival and aberrant IGF-1 signalling has been implicated in neurodegenerative diseases. Here, Aghanoori et al. extended the existing literature by showing that IGF-1 levels are suppressed by hyperglycaemia in sensory neurons of robust type 1 and type 2 diabetic rodent models. This in turn compromises mitochondrial bioenergetics and impairs axonal regeneration. Importantly, their findings support the view that the activation of IGF-1 or its upstream regulator CEBPβ may provide effective therapeutic strategies for the treatment of diabetic neuropathy across diabetes types.

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Reference. Aghanoori MR, Agarwal P, Gauvin E, Nagalingam RS, Bonomo R, Yathindranath V, Smith DR, Hai Y, Lee S, Jolivalt CG, Calcutt NA, Jones MJ, Czubryt MP, Miller DW, Dolinsky VW, Mansuy-Aubert V, Fernyhough P. CEBPβ regulation of endogenous IGF-1 in adult sensory neurons can be mobilized to overcome diabetes-induced deficits in bioenergetics and axonal outgrowth. Cell Mol Life Sci. 2022 Mar 17;79(4):193. doi: 10.1007/s00018-022-04201-9. PMID: 35298717; PMCID: PMC8930798.
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