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Insulin-like growth factors (IGFs) prevent diabetic peripheral neuropathy despite unabated hyperglycemia: Why hyperglycemia interventions fail in clinical trials?

Sensory, motor and autonomic neuropathy caused by dying-back axonopathy are common complications in diabetes that may result in limb amputations, impotence, loss of bladder control, increased risk of cardiovascular mortality and other disturbances. Present therapy is palliative; the development of meaningful treatments requires improved understanding of the pathogenesis of axonopathy. The dominant hypothesis for decades has been the hyperglycemia results in polyol accumulation, protein glycation, accumulation of advanced glycation end product (AGE) and subsequent injury to peripheral nerves. The alternative hypotheses were tested: neuropathy arises mainly as a consequence of a decline in combined neurotrophic insulin and IGF activities and; neuropathy can be prevented by restoration of IGF levels irrespective of hyperglycemia. IGF levels decline progressively with aging, and more rapidly in obese, T1D and T2D patients. Diabetic rats have reduced IGF gene expression in nerves, spinal cord, brain and livers. Subcutaneous administration of IGF prevented multiple manifestations of sensory, motor and autonomic neuropathy despite unabated hyperglycemia in diabetic rats. IGF blockade in non-diabetic rodents mimics diabetic neuropathy. New results show that insulin provides additive neurotrophic support for the nervous system via pathways separate from glucoregulation. Clinical trial end-points to prevent diabetic neuropathy in T2D should be directed at increasing IGF levels and reducing insulin resistance, whereas hyperglycemia is an unreliable end-point. Indeed, intensive anti-hyperglycemic therapy in T2D, which comprises 90% of diabetic cases, does not prevent microvascular disease (neuropathy, nephropathy and retinopathy).

Biography

Douglas N Ishii has completed his BA degree in Biochemistry at University California, Berkeley, and has completed his PhD in Pharmacology from Stanford University School of Medicine, and conducted Post-doctoral studies in Neurobiology at the same institution. He is presently a Professor in Biomedical Sciences at Colorado State University. He has served on many scientific review panels. He is a Founder of Aurogen Inc., a biotechnology company dedicated to developing new treatments for Alzheimer's disease.

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