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WHY CLINICAL TRIALS SHOW THAT STRICT GLUCOSE REGULATION DOES NOT PREVENT DIABETIC COMPLICATIONS IN T2D: EVIDENCE SUPPORTING AN ALTERNATIVE HYPOTHESIS FOR PATHOGENESIS

Statement of Problem: A meta-analysis of clinical trials with 34,533 T2D patients shows that intensive lowering of glucose levels does not prevent neuropathy, retinopathy, nephropathy, cardiovascular death, nor excess mortality. Exposing patients to adverse effects from unbeneficial drugs is unjustified, yet remains standard therapy. An alternative hypothesis for pathogenesis of diabetic complications is greatly needed to develop meaningful rational therapies.

Methodology & Theoretical Orientation: Following discovery that insulin and insulin-like growth factors (IGFs) are neurotrophic factors, the inter-related hypotheses were developed that loss of insulin and IGF activities is the dominant cause of diabetic neuropathy, and that replacement of such activities should ameliorate diabetic complications irrespective of unabated hyperglycemia. These hypotheses were tested by infusing IGFs, insulin, or their combination into diabetic rats to determine whether neuropathy is alleviated under conditions in which hyperglycemia is not prevented.

Conclusion & Significance: IGF gene expression is reduced in peripheral nerves, brain and spinal cord in diabetes. Replacement IGF infusion prevented impaired sensory and motor nerve regeneration, hyperalgesia, abnormal ultrastructure in autonomic axons, loss of epidermal nerve fiber density, and poor gastric wound healing, but did not diminish hyperglycemia. To study mechanism, insulin and/or IGF was infused into diabetic rat brains under conditions that did not reduce hyperglycemia. A decrease in total mRNA, protein, and DNA levels was associated with brain atrophy and impaired learning/memory in diabetic rats. Insulin and IGF *i.c.v.* infusion prevented all of these disturbances despite unabated hyperglycemia. Insulin and IGFs are master switches controlling the levels of hundreds of proteins in tissues; loss of protein regulation, not hyperglycemia, is proposed as the most likely pathogenic cause for diabetic complications. Governments should manufacture clinical grade IGF (off-patent). Clinical trials are urgently needed to test insulin/IGF therapy.

Biography

Douglas N Ishii was born in US concentration camp at the onset of WWII, and grew up in a government housing project in San Francisco. He received a B.A. Biochemistry from Univ. Calif. Berkeley, a Ph.D. Pharmacology from Stanford Univ. Medical Sch., and conducted postdoctoral work in Neurobiology at Stanford. He became Assistant than Associate Prof. Pharmacology at Columbia Univ. NYC. He is a Professor of Biomedical Sciences at Colorado State Univ. He served on various scientific study sections for National Science Foundation, National Institutes of Health, and the Juvenile Diabetes nternational Foundation. Press coverage on his laboratory's research on pathogenesis of diabetic neurological complications, and causation of brain atrophy in Alzheimer's disease, includes articles in Der Spiegel, Hong Kong Standard, NY Times, LA Times, Denver Post, Chicago Tribune, ABC News, Forbes News, USA Today, National Public Radio, and elsewhere. Nineteen patents were awarded based on this research.

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