Why clinical trials that reduce glucose levels *fail to prevent* complications in diabetic patients: Tests support an alternative hypothesis for pathogenesis

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Abstract

Statement of Problem: Meta-analysis of outcomes on 34,533 Type 2 diabetic patients shows that intensive lowering of glucose levels does *not* prevent neuropathy, retinopathy, nephropathy, cardiovascular death, nor excess mortality (1). Nor does lowering of glucose levels prevent complications in approximately 40% of Type 1 patients. Exposing patients to adverse effects from unbeneficial drugs is unjustified, yet remains standard therapy. The development of meaningful novel treatments awaits an alternative hypothesis for pathogenesis of diabetic complications.

Methodology and Theoretical Orientation: Insulin and insulin-like growth factors (IGFs) are neurotrophic factors (2-4). The inter-related hypotheses were developed that diminished insulin and IGF activities is the dominant cause of neurological complications, and that replacement of such activities should ameliorate diabetic complications irrespective of unabated hyperglycemia (5). 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 remains unabated.

Conclusion & Significance: IGF mRNA levels are reduced in peripheral nerves, brain and spinal cord in diabetes (6, 8). 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 despite undiminished hyperglycemia (7-10). Tiny doses of insulin and/or IGF were 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 such disturbances despite unabated hyperglycemia (11-13). Insulin and IGFs are master switches controlling the levels of hundreds of proteins in brain; 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.

Key Publications

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5. Ishii DN (1995) Implications of IGFs in Pathogenesis of Diabetic Neuropathy. Brain Research Reviews **20**: 47-67.
6. Wuarin L, Guertin DM and Ishii DN (1994) Early Reduction in Insulin-Like Growth Factor Gene Expression in Diabetic Nerve. Experimental Neurology **130**: 106-114.
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8. Zhuang H-X, Wuarin L, Fei Z-J and Ishii DN (1997) Insulin-like Growth Factor (IGF) Gene Expression Is Reduced in Neural Tissues and Liver from Rats with Non-Insulin-Dependent Diabetes Mellitus, and IGF Treatment Ameliorates Diabetic Neuropathy. Journal of Pharmacology & Experimental Therapeutics **283**: 366-374.
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12. Lupien SB, Bluhm EJ and Ishii DN (2006) Effect of IGF-I on DNA, RNA, and Protein Loss Associated With Brain Atrophy and Impaired Learning in Diabetic Rats. Neurobiology of Disease **21**: 487-495.
13. Serbedzija P, Madl JE and Ishii DN (2009) Insulin and IGF-I Prevent Brain Atrophy and DNA Loss in Diabetes. Brain Research **1303**: 179-94.

Biography



Douglas N. Ishii was born in a 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 International 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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