Gerald J Prud'homme, J Diabetes Metab 2017, 8:7 (Suppl)
DOI: 10.4172/2155-6156-C1-065

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TREATMENT OF HUMAN PANCREATIC BETA CELLS WITH A COMBINATION OF GAMMA-AMINOBUTYRIC ACID (GABA) AND GLP-1 AMELIORATES CELL SURVIVAL AND PROLIFERATION

An effective therapy for type 1 diabetes (T1D) requires the protection of pancreatic beta cells against autoimmunity (immunosuppression and/or anti-inflammatory activity) and beta-cell proliferation or regeneration. No current treatment achieves both goals in a clinical setting. The incretin hormone GLP-1 is effective in the treatment of type 2 diabetes (T2D), but not T1D. Recent studies by us and others have shown that GABA protects beta cells against autoimmune injury and induces their regeneration in mice. In this study, we investigated the effects of these drugs on human islets cells, and compared their response to rodent insulinoma cell lines. We found that GABA increases SIRT1 and Klotho (mRNA and protein), and prevents apoptosis induced by high glucose levels or inflammatory cytokines. Importantly, both Klotho and SIRT1 inhibit the activation of NF-kB. The NF-kB inflammatory pathway provokes beta-cell apoptosis, such that its blockade is protective. We show that a GLP-1 receptor (GLP-1R) agonistic drug ameliorates the effects of GABA in some assays. However, we observed that a GLP-1R agonist does not stimulate human beta-cell proliferation, whereas GABA does promote proliferation. We conclude that GABA, especially when combined with GLP-1, effectively protects human beta islet cells against glucotoxicity and other injuries, and that GABA (but not GLP-1) stimulates their proliferation. These observations suggest that GABA+GLP-1 therapy will be effective in human T1D, due to a combination of anti-apoptotic, anti-inflammatory and proliferative/regenerative effects.

Biography

Gerald J Prud'homme is a Professor in the Department of Laboratory Medicine and Pathobiology at the University of Toronto, and Clinician-Scientist at St. Michael's Hospital, Toronto. He received his MD degree from the University of Ottawa, Canada (1977) and subsequently specialized in Pathology. He is a Research Fellow at the Institute of Immunology, University of Toronto, the Scripps Research Institute and the McGill Cancer Centre (McGill University, Montreal). Subsequently (1985-2002), he worked as a Scientist and Pathologist in the Department of Pathology, McGill University. His main research interests are in the areas of immunotherapy of autoimmune diseases and cancer therapy.

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