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Gamma-aminobutyric acid (GABA) and GLP-1 treatment blocks the activation of the NF-kB inflammatory pathway and promotes the survival and proliferation of human pancreatic beta cells

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The inhibition of autoimmunity against pancreatic beta cells and the promotion of the proliferation/regeneration of these cells are major goals in the treatment of type 1 diabetes (T1D). Gamma aminobutyric acid (GABA) and the incretin hormone GLP-1 (currently used to treat type 2 diabetes) are candidate drugs to mediate these effects. In rodents, therapies with these agents induce beta-cell proliferation, reduce apoptosis, and increase beta-cell mass. Here, we examined the effects of these agents on human islet cells and insulinoma cell lines. We observed that GABA treatment of beta cells increases the expression of SIRT1 and Klotho, and protects against apoptosis due to glucotoxicity or inflammatory cytokines. Notably, both SIRT1 and Klotho block activation of the NF-kB inflammatory pathway. NF-kB contributes to beta cell apoptosis, and inhibiting this pathway appears to be protective. We demonstrate that a GLP-1 receptor (GLP-1R) agonist augments the activity of GABA in some (but not all) of these protective effects. Furthermore, we report that a GLP-1R agonist fails to induce human beta-cell proliferation (unlike findings in mice) but, in contrast, GABA has broader effects and induces proliferation. These results support the use of GABA as an agent to induce beta-cell regeneration. In conclusion, GABA and GLP-1, especially in combination, were effective at protecting human beta islet cells against glucotoxicity and other injuries, and GABA stimulated their proliferation. These findings suggest that GABA/GLP-1 therapy has potential application in the treatment of human T1D

Biography

Gerald J. Prud'homme is Professor in the Department of Laboratory Medicine and Pathobiology, University of Toronto, Canada; and Clinician-Scientist, Keenan Research Centre for Biomedical Science (St. Michael's Hospital), Toronto. He holds an M.D. degree, and is a specialist in pathology. He was a research fellow at the Charles H. Best Institute and Institute of Immunology, University of Toronto, the Scripps Research Institute (La Jolla, California), and the McGill Cancer Centre (Montreal). His research interests are in the areas of diabetes and autoimmune diseases. He is a member of the Banting and Best Diabetes Centre in Toronto

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