JQ1 Epigenetic Modulation of Pancreatic Beta-Cells (INS-1) Normalizes Glucose Sensitivity Under Hyperglycemia: Therapeutic Preventive Implications for Type II Diabetes Mellitus

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Chronic hyperinsulinemia and insulin resistance are prequels to type II diabetes mellitus. Previous studies from our laboratory have demonstrated that the Bromodomain-and-Extra-Terminal protein-inhibitor JQ1 increases fatty acid oxidation in clonal pancreatic beta-cells—INS-1. The present research investigates the effect of JQ1 as a co-repressor of transcription within the BET domain on the glucose sensitivity of INS-1 cells under hyperglycemic conditions. INS-1 cells were pre-treated with dimethyl-sulfoxide-based 400-nM JQ1 for 3 days and cultured for 5 days in RPMI 1640 media. Subsequently, INS-1 cells were pre-incubated in a modified Krebs-Henseleit buffer before adding test solutions—1-12 mM glucose. Samples for insulin release and cellular content were measured using a Homogeneous Time-Resolved Fluorescence insulin assay. Three-day treatment with JQ1 reduced secretion at 4 mM glucose to basal level while maintaining the right-shifted concentration-dependent GSIS—effect described herein for the first time. Total insulin content and release as its percentage were also measured, indicating a higher TIC and lower percentage use in treated cells. Additionally, lipid concentration was photographically-fluorescent analyzed, showing significant depletion of lipid droplets in treated cells. Results imply that epigenetic modulation of pancreatic beta-cells with JQ1 beneficially alters signal-transduction pathways that maintain insulin-glucose homeostasis by ameliorating glucolipotoxicity through the preservation of a low-GSIS basal level, increment of GSIS maximum capacity, delay of GSIS cuspid level, more efficient spend of TIC, and diminished lipid accumulation by increased FA oxidation—thereby suggesting JQ1 returning hyperglycemic beta-cells to physiological conditions.

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