

Control of Inflammation in Pancreatic β -cells: Role of Arylpyrazole Compounds

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Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease characterized by the destruction of the insulin-producing pancreatic islet β -cells leading to elevations in blood glucose levels. Destruction of islet β -cells results from immune-cell infiltration into the islets and ensuing production of pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β), from such cells. IL-1 β signals through receptors on the β -cell surface, which leads to the production of chemoattractant proteins called chemokines directly from the β -cells. This process produces a continuous inflammatory response that leads to β -cell death and dysfunction associated with the development of T1DM. Thus, novel therapeutic interventions that reduce or slow the progression of the inflammatory response within the pancreatic β -cells would be beneficial for treatment or cure of T1DM. One approach to reduce inflammation in a variety of human diseases is the administration of synthetic glucocorticoids. Glucocorticoids act through an intracellular receptor to elicit anti-inflammatory actions. However, current glucocorticoid receptor agonists impair β -cell function, which limits their clinical effectiveness. Thus, the current project investigated whether two non-steroidal arylpyrazole compounds were able to mimic the anti-inflammatory effects of glucocorticoids by suppressing known inflammatory responses in pancreatic β -cells. Using luciferase-based reporter assays as a measure of inflammatory gene activation revealed that Arylpyrazole 4 (AP4) significantly suppressed maximal IL-1 β response starting at 100nM whereas Arylpyrazole 5 (AP5) did not significantly suppress the IL-1 β response. When applied to a 3xGRE promoter, AP4 significantly activated the GRE at 100nM dosage whereas AP5 showed no activation of the GRE. The difference between these two compounds was an alcohol functional group present in the AP4 versus the ketone in AP5. We conclude that the difference in anti-inflammatory activity of AP4 and AP5 are due to distinct structure-function relationships with the ligand (AP) and glucocorticoid receptor. These preliminary findings will serve as the foundation for future investigation as to how the arylpyrazole scaffold can be modified to produce anti-inflammatory activities in pancreatic β -cells without suppressing insulin secretion.