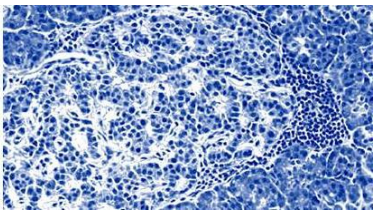
nPOD
Network for Pancreatic Organ Donors with Diabetes



Functional Role of inositol 1,4,5-trisphosphate receptor in Pancreatic β Cell Phatophysiology

AUTHORS

Jun Shu, Jessica Gambardella, Xue-Liang Du, Gaetano Santulli
Albert Einstein College of Medicine – Montefiore University Hospital, New York, NY,

PURPOSE

According to the classic paradigm, insulin secretion is triggered by the influx of extracellular calcium (Ca^{2+}) via voltage-dependent channels, leading to the fusion of insulin granules. Instead, the mechanisms involved in Ca^{2+} mobilization from internal stores are less defined. The main intracellular Ca^{2+} release channels are inositol 1,4,5-trisphosphate receptor (IP3R) and ryanodine receptor (RyR), whereas Ca^{2+} is returned to the *ER* primarily by the activity of the sarco/*endoplasmic reticulum* Ca^{2+}ATPase (SERCA) pump. We and others recently demonstrated the importance of RyR in type 2 diabetes mellitus (T2DM), showing that it is essential in glucose-stimulated insulin secretion (GSIS). Conversely, the exact role of IP3R in GSIS remains not fully understood and represents the main aim of this study.

METHODS

We performed functional studies *in vivo* (mouse models), *ex vivo* (isolated murine and human islets), and *in vitro* (clonal β cells).

SUMMARY OF RESULTS

Three isoforms of IP3R have been identified in mammalian cells. Channel opening is stimulated by the binding of second messenger IP3 and by changes in Ca^{2+} concentrations. Studies in rodent and human samples indicate that β cells express all IP3R isoforms. We demonstrated that the expression of all isoforms is significantly increased in human islets from diabetic donors compared with non-diabetic individuals. These results were confirmed in diabetic mice. Moreover, pancreatic β cells from diabetic patients exhibited dysmorphic and dysfunctional mitochondria, with markedly altered Ca^{2+} uptake. Similar features were found in clonal β cells chronically exposed to high glucose. *In vitro*, overexpression of IP3Rs was associated with impaired GSIS, whereas IP3R silencing improved β cell function, mitochondrial Ca^{2+} uptake and function, ER stress, and insulin release in response to different secretagogues.

CONCLUSIONS
Taken together, our data indicate that IP3Rs are upregulated in human islets from diabetic donors, leading to mitochondrial dysfunction and pancreatic β cell failure, identifying in these intracellular Ca^{2+} release channels a novel therapeutic target to treat diabetes.