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**Glucose inhibits glucagon secretion of mice with alpha cell specific deletion of KATP channels**

**M. Parambath**, B. Lai, H. Chae, E. Gatineau, P. Gilon;
Pôle d'Endocrinologie, Diabète et Nutrition, Université Catholique de Louvain, Brussels, Belgium.

**Background and aims:** Glucose stimulates insulin and somatostatin (SST) secretion by closing β- and δ-cell $K_{ATP}$ channels. By contrast, it inhibits glucagon release by largely unknown mechanisms. The role of α-cell $K_{ATP}$ channels in the control of glucagon release and their implication in the glucagonostatic effect of glucose are hotly debated. They are particularly difficult to evaluate because α-, β- and δ-cells mutually influence their secretions. To study the role of α-cell $K_{ATP}$ channels in the control of glucagon release, we generated α-$K_{ATP}$KO mice that lack $K_{ATP}$ channels specifically in α-cells and compared their glucagon secretion in response to a change of the glucose concentration between 1 and 7 mM to that of control islets. To evaluate the role of SST that is released from δ-cells upon $K_{ATP}$ channel closure, we used two mouse models that lack SST, i.e. SSTKO and SSTKO/ α-$K_{ATP}$KO mice.
**Materials and methods:** The following mouse models were used: Kir6.2flox (control), α-$K_{ATP}$KO (GluCre x Kir6.2flox), SSTKO and SSTKO/α-KATPKO. To measure $[Ca^{2+}]_c$ (by confocal microscopy) in α-cells within islets, we used the following mice expressing the fluorescent $Ca^{2+}$ sensor, GCamP6, in α-cells: α-GCamP6 (GluCre x LSL-GCamP6) and α-GCamP6/α-KATPKO (GluCre x Kir6.2flox x LSL-GCamP6). All experiments were performed in the presence of a 6 mM amino acid mixture (2 mM alanine, 2 mM arginine and 2 mM glutamine).
**Results:** Increasing the glucose concentration from 1 to 7 mM inhibited glucagon release of α-$K_{ATP}$KO and control islets expressing or not SST, suggesting that glucose can control glucagon secretion independently of α-cell $K_{ATP}$ channels and SST. These changes in glucagon secretion were associated with parallel but modest changes in α-cell $[Ca^{2+}]_c$. The addition of the $K_{ATP}$ channel opener, diazoxide (250 µM), at 1 mM glucose suppressed glucagon release and decreased α-cell $[Ca^{2+}]_c$ of control islets. Interestingly, it stimulated glucagon secretion and increased α-cell $[Ca^{2+}]_c$ of α-$K_{ATP}$KO islets, whereas it was without effect in SSTKO/α-$K_{ATP}$KO islets. This suggests that pharmacological opening of α-cell $K_{ATP}$ channels suppresses glucagon release whereas opening of δ-cell $K_{ATP}$ channels stimulates glucagon secretion by alleviating the glucagonostatic effect of SST released by δ-cells.
**Conclusion:** Glucose can inhibit glucagon secretion independently of α-cell $K_{ATP}$ channels and independently of SST. The strong inhibitory effect of glucose associated with a very modest decrease in α-cell $[Ca^{2+}]_c$ suggests that glucose controls glucagon release by a mechanism that is partly independent from α-cell $[Ca^{2+}]_c$ changes. The observation that diazoxide stimulates glucagon secretion of α-$K_{ATP}$KO islets but not that of SSTKO/α-$K_{ATP}$KO islets illustrates a strong tonic inhibition of glucagon release by SST, even at low glucose.
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**Recombinant PSP/reg treatment improves beta cell function in islets isolated from glucose intolerant and type 2 diabetic donors**

**I. Louvet**[1], M. Moreno-Lopez[1], A. Acosta-Montalvo[1], V. Gmyr[1], J. Kerr-conte[1], T. Reding[2], C. Saponaro[1], F. Pattou[1], R. Graf[2], C. Bonner[1];
[1]Université de Lille, CHU Lille, Institut Pasteur de Lille, Inserm UMR1190 - EGID, Lille, France, [2]Department of Surgery, University Hospital Zurich, Zurich, Switzerland.

**Background and aims:** Pancreatic islet dysfunction and demise are key characteristics of type 1 diabetes (T1D), type 2 diabetes (T2D), and HNF1A-MODY, respectively. Pancreatic Stone Protein / Regenerating Protein (PSP/reg) is regulated at the transcription level by the Hepatocyte Nuclear Factor family of proteins and physiologically secreted from pancreatic acinar cells. Upon focal or systemic extra-pancreatic inflammation, such as sepsis, PSP/reg is strongly increased, but also highly elevated in the serum of T1D, TD2, and HNF1A-MODY patients. Although, PSP/reg is expressed and induced in islets of diabetic mice, the mechanisms involved remain largely unknown. Therefore, the aim of this study was to investigate the expression and regulation of PSP/reg in the human pancreas and islets isolated from donors covering a wide spectrum of metabolic disease compared to normoglycemic controls.
**Materials and methods:** PSP/reg protein expression was analysed from human paraffin embedded pancreatic sections and isolated islets embedded in histogel by immunofluorescence. PSP/reg gene and protein expression was analysed by qPCR and Western Blotting, respectively. Perifusion techniques were used to determine glucose-stimulated-insulin-secretion (GSIS) in islets isolated from donors with glucose intolerance or T2D in response to a chronic treatment with recombinant PSP/reg (rPSP/reg).
**Results:** PSP/reg protein was highly enriched in the acinar cells of all donor pancreata studied. Islets embedded in histogel revealed that PSP/reg colocalized with insulin in beta cells, somatostatin in delta cells and, to a lesser extent, with glucagon in alpha cells. Of note, PSP/reg protein expression was significantly induced in islets isolated from T2D donors with obesity compared to those of obese (normoglycemic), glucose intolerant and normoglycemic donors. Moreover, the chronic treatment of rPSP/reg (24 h) enhanced both, first and second phase GSIS from islets isolated from glucose intolerant donors, while only the second phase was enhanced from those of T2D donors.
**Conclusion:** Collectively, these data indicate that PSP/reg may play an important role in preserving beta cell function during the early stages of the disease. They also suggest that rPSP/reg could be a promising therapy for the treatment of diabetes, but further studies in diabetic mice to determine its efficacy to reduce hyperglycemia and improve islet function are warranted.
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**Functional genomics highlights type 2 diabetes-associated purinergic receptor P2RY1 as a new modulator of insulin secretion in humans**

**A. Dance**[1], M. Derhourhi[1], M. Boissel[1], M. Marre[2,3], G. Charpentier[4], A. Khamis[1,5], P. Froguel[1,5], A. Bonnefond[1,5];
[1]59, UMR1283 EGID, Lille, France, [2]75, Inserm U1138, Centre de Recherche des Cordeliers, Paris, France, [3]75, CMC Ambroise Paré, Paris, France, [4]91, CERITD (Centre d'Étude et de Recherche pour l'Intensification du Traitement du Diabète), Evry, France, [5]Department of Metabolism, Imperial College, London, UK.

**Background and aims:** Genome-wide association studies (GWAS) have shown that the *P2RY1* locus is associated with type 2 diabetes (T2D) risk and with glucose levels. P2RY1 is a G-protein coupled receptor (GPCR) activated by ATP and ADP, which is highly expressed in pancreatic islets, particularly in β cells where, ATP / ADP stimulate insulin secretion by activating the ATP-dependent potassium channels. Through functional genetics, we aimed to analyze the putative contributions of genetic variants of *P2RY1* to T2D risk and to other metabolic traits. We then characterized the downstream signaling pathways of P2RY1 in human pancreatic beta cells and deciphered its putative role in insulin secretion.
**Materials and methods:** *P2YR1* was sequenced in 6,348 French adults including cases with T2D and normal glucose controls. To assess the functional effect of each identified variant, we performed 1/ luciferase assays (NFAT-RE system) on HEK293 cells overexpressing each variant, followed by P2YR1 activation by increasing