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Imeglimin Protects Ins-1 Cells And Human Islets Against High Glucose- And High Fructose-induced Cell Death By Inhibiting The Mitochondrial PTP Opening

Author Block: SANDRINE LABLANCHE, EMILY TUBBS, CÉCILE COTTET-ROUSSELLE, FREDERIC LAMARCHE, ANAÏCK MOISAN, VIRGINIE PERSOONS, PIERRE Y. BENHAMOU, **SOPHIE HALLAKOU-BOZEC**, ERIC FONTAINE, *Grenoble*, *France*, *Saint-Martin d'Hères*, *France*, *Saint Ismier*, *France*, *St Ismier*, *France*, *Lyon*, *France*

Abstract:
Imeglimin (IME) is a novel glucose-lowering agent improving insulin secretion in response to glucose and insulin sensitivity by targeting mitochondrial bioenergetics. IME is currently in phase 3 in Japan. The toxicity of high glucose or fructose concentrations in INS-1 cells was linked to the opening of the permeability transition pore (PTP), a mitochondrial channel involved in cell death. IME has been shown to prevent PTP opening in human endothelial cells under oxidative stress. This study investigated whether IME could also prevent PTP opening and cell death induced by high glucose or fructose concentrations in INS-1 cells and human pancreatic islets. PTP status in intact cells was assessed by confocal microscopy by measuring mitochondrial membrane potential (TMRM) and NAD(P)H (autofluorescence). Cell viability was measured by flow cytometry. In INS-1 cells and human islets, 30 mM Glucose or 2.5 mM Fructose for 24h led to PTP opening (increase in the NAD(P)H/TMRM ratio), this phenomenon being prevented by 100µM IME. Compared to normal glucose concentration (100%), cell viability significantly decreased ($p<0.05$) in cells exposed to 30 mM Glucose (76±5% and 47±18% in INS-1 cells and human islets, respectively) and to 2.5 mM Fructose for 72h (78±3% and 35±11% in INS-1 cells and human islets, respectively) but remained unchanged when these cells were preincubated with 100µM IME (in 30mM glucose: 94±3% and 98±3% / in 2.5mM fructose: 96±4% and 79±6% in INS-1 cells and human islets, respectively). We conclude that (i) IME is able to prevent high glucose and fructose-triggered cell death through an inhibition of PTP opening and (ii) a PTP-targeted strategy can prevent beta cell death. In addition to its beneficial effect on beta cell function, IME may have the potential to preserve beta cell mass in a dysmetabolic environment via its inhibitory effect on PTP opening.
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2451 Crystal Drive, Suite 900
Arlington, VA 22202

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