

## A ROLE FOR THE TRANSIENT RECEPTOR POTENTIAL MELASTATIN 5 (TRPM5) CHANNEL IN GLUCOSE-INDUCED OSCILLATIONS IN INTRACELLULAR CALCIUM AND MEMBRANE POTENTIAL IN THE PANCREATIC BETA CELL.

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The role of the Ca<sup>2+</sup>-activated non-selective cation channel TRPM5 in the electrical activity of the pancreatic beta cell was investigated using a *Trpm5*<sup>-/-</sup> mouse. TRPM5 is selectively expressed in beta cells from the pancreatic islet and *Trpm5*<sup>-/-</sup> mice display an impaired glucose tolerance caused by a reduced glucose-induced insulin release from pancreatic islets. We could show that a Ca<sup>2+</sup>-activated non-selective cation current is significantly reduced in beta cells from *Trpm5*<sup>-/-</sup> mice. To gain a mechanistic insight we measured dynamics of the intracellular Ca<sup>2+</sup> concentration [Ca<sup>2+</sup>]<sub>IC</sub> and membrane potential (V<sub>m</sub>) in intact islets. Islets from both phenotypes displayed an oscillatory increase in [Ca<sup>2+</sup>]<sub>IC</sub> after stimulation with 10mM glucose, but *Trpm5*<sup>-/-</sup> islets clearly showed an overall reduced frequency in [Ca<sup>2+</sup>]<sub>IC</sub> oscillations. Through a Fourier analysis, we could distinguish 3 types of oscillating patterns in WT islets: either slow or fast oscillations or a mixed pattern consisting of fast oscillations superimposed on slow ones. *Trpm5*<sup>-/-</sup> islets completely lacked the fast oscillations and displayed a significantly and highly reduced frequency of fast oscillations in the mixed pattern. The interburst interval in between fast oscillations is significantly shorter and is characterized by a higher velocity of depolarization. Our data indicate that TRPM5 contributes to the slow depolarization towards the threshold potential in the interburst interval during oscillatory changes of [Ca<sup>2+</sup>]<sub>IC</sub> and V<sub>m</sub>. Deletion of TRPM5 prolongs this interval, resulting in slower oscillations in V<sub>m</sub> and in [Ca<sup>2+</sup>]<sub>IC</sub>. This leads to a reduced glucose-induced insulin release and consequently to a less efficient glucose clearance in *Trpm5*<sup>-/-</sup> mice. As such, TRPM5 might be a novel target in the treatment of type II diabetes.