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Beta-cell-specific expression of glucagon-like peptide 1 (GLP-1) and activated muscarinic receptor (M3R) improves pig islet secretory function

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Background & Aims: Pig islets represent a promising alternative to human islet transplantation since they can be obtained in large quantities without raising ethical questions. Insulin produced by porcine beta-cells differs from human insulin by only one amino acid and has long been used to treat diabetic patients. However, pig islets show a relatively weak response to glucose stimulation. When isolated pig islets are stimulated by increasing glucose concentration, the increase in insulin secretion is between 1.5 and 3-fold. In comparison, insulin secretion is increased by 12 to 16-fold when human, primate or rodent islets are challenged with a similar increase in glucose concentration. This property of pig islets has sometimes raised doubts regarding their usefulness as a treatment for diabetes. In particular, the lower response to glucose stimulation of porcine islets compared to human islets leads to the need to transplant a high number of islets to adequately correct human glucose levels. It is thus crucial to have better understanding of pig beta-cell physiology and to seek pathways that can improve pig islet insulin secretion.

Material & Methods: GLP-1 and activated M3R expression in primary pig beta-cells was induced by exposing isolated islets to adenoviral vectors carrying sequences encoding GLP-1, M3R or both proteins. Insulin secretion from control and transgenic islets was evaluated by static incubation and dynamic perfusion experiments 48 hours following infection.

Results: As shown in figure 1, stimulation index in control islets was around 3. Expression of GLP-1 alone had little to no effect on insulin secretion from neonatal and adult islets. Islets expressing M3R showed increased glucose-stimulated insulin secretion (stimulation index 5.4 and 4.1 in neonates and adults respectively). Interestingly, neonatal islets co-expressing GLP-1 and M3R showed a synergetic response in terms of insulin secretion since their stimulation index was 7.3. This effect was also observed although to a lesser extent in adult islets (stimulation index 5.5)

Conclusion & Perspectives: Isolated pig islets show poor secretory response upon stimulation. Insulin secretion from both neonatal and adult islets can be increased by co-expression of GLP-1 and activated M3R in primary beta-cells. GLP-1 increases cytoplasmic cAMP thus activating protein kinase A whereas activation of M3R leads to activation of protein kinase C. It thus seems that concomitant activation of these protein kinases would be beneficial for increasing insulin secretion from pig islets and rendering them more efficient in controlling glycaemia in graft recipients. Transgenic pigs with beta-cell specific activation of these two pathways would be better donors for islet xenotransplantation.

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