Opposite functions of beta-arrestin2 for the potentiation of insulin secretion by GLP-1 and GIP

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Background and aims : The scaffold protein beta-arrestin2 (ARRB2) is known to uncouple G protein coupled receptors (GPCRs) from the G protein and to recruit new signaling pathways (such as ERK1/2). It has been reported in non beta cells a direct interaction of ARRB2 with the GLP-1 receptor (GLP-1R), while its interaction with the GIP receptor (GIPR) is unclear. Our aim was to determine if ARRB2 is involved in both incretin receptor signaling in mouse beta cells.

Materials and methods : The experiments were carried out in beta cells from five-month-old Arrb2+/+ and Arrb2-/- male mice. cAMP production (CAMPS-epac), endogeneous PKA (AKAR3) and ERK1/2 (EKAR) activations were measured by live microscopy after adenoviral infection of cells with FRET-based sensors of interest. Epac2 (Epac2-GFP) recruitment to the plasma membrane was assessed by TIRF microscopy. Cytosolic Ca2+ concentration ([Ca2+]c) was measured by Fura2-LR.

Results: The genetic deletion of Arrb2 in mice was associated with a better oral glucose tolerance and a concomitant increase in plasma insulin concentration ($p<0.05$) despite an impaired i.p. glucose tolerance and a decrease in beta cell mass, suggesting a greater incretin effect. However, opposite effects in response to both incretin hormones were observed in Arrb2-/- islets for insulin secretion. Whereas insulin secretion from Arrb2-/- islets was larger with physiological concentrations of GLP-1 (1-10pM GLP-1; $p<0.01$), it was reduced by 50% in response to GIP (100pM-10nM, $p<0.01$). When ARRB2 (ARRB2-GFP) was re-expressed in Arrb2-/- beta cells, insulin secretion in response to GLP-1 or GIP was restored to a similar level than in Arrb2+/+ islets. The larger insulin release induced by 10pM GLP-1 in Arrb2-/- beta cells was associated with an increased cAMP production, PKA activation, and [Ca2+]c (oscillations frequencies and mean level), while the Epac2 recruitment remained unchanged. In contrast, GLP-1-induced activation of ERK1/2 was strongly decreased (~50%, $p<0.05$) in Arrb2-/- beta cells. Unexpectedly, under GIP stimulation, the cAMP (cAMP, PKA, Epac2), [Ca2+]c and ERK1/2 signaling pathways were similar in Arrb2+/+ and Arrb2-/- beta cells. Additionally, GLP-1 compared to GIP induced PKA long lasting activation after removal of the stimulation (>25 min vs 5min) suggesting slow versus fast recycling receptors, respectively, that were independent of ARRB2 expression. Finally, glucolipotoxic conditions induced a 20% decrease of ARRB2 expression in human islets ($p<0.05$).

Conclusion: Our study revealed a differential role of ARRB2 in GLP-1R and GIPR signalling, and therefore a specificity of action for two GPCR positively coupled to cAMP. ARRB2 contributes to a partial uncoupling of cAMP/PKA signalling in the pM range of GLP-1, and consequently reduced insulin secretion. By contrast, ARRB2 plays a crucial role in GIP potentiation of insulin secretion that is independent and/or distal to cAMP, [Ca2+]c and ERK1/2 changes. Therefore, any variation in the expression of ARRB2, as observed in diabetic states, should functionally impact the incretin effect.