**The lack of β2 adrenoceptors in mice results in glucose intolerance and impaired insulin secretion**

**Gaetano Santulli, Angela Lombardi, Daniela Sorriento, Antonio Anastasio, Salvatore Iovino, Carmine Del Giudice, Bruno Trimarco, Francesco Begunioti, Pietro Formisano, Claudia Miele, Guido Iaccarino**

**“Federico II” UNIVERSITY & CNR, Naples - ITALY**

**Background:**
- The reciprocal regulation of Sympathetic Nervous System and Insulin relays on molecular mechanisms that are not fully understood;
- β2-adrenergic receptors (β2AR) are known to be involved in insulin production and peripheral glucose uptake, but their role in development of diabetes is not clear.1,2

**Aim of the study:**
To evaluate the role of β2 AR in insulin secretion and glucose homeostasis.

**Methods:**
We characterized the metabolic phenotype of 6 month old mice with deletion of the β2 AR gene. β2AR KO mice were generated by one-step embryonic stem cell targeting, and crossed onto a C57BL/6J background. Indeed, β2 AR mice exhibited slightly increased fasting blood glucose levels compared to wild type (WT) mice. However, glucose loading (2 g/kg) rendered the β2 AR mice significantly more glycemic during the following 120 min compared to WT mice (Fig.2A). This abnormality indicates that β2AR ablation is sufficient to impair glucose tolerance in mice. Interestingly, we observed that β2AR KO mice also displayed a defect in insulin secretion, (Fig.2B) but presented enhanced peripheral insulin sensitivity (Fig.2C).

**Results:**
- **β2 KO mice**: β2 AR KO mice exhibited slightly increased fasting blood glucose levels compared to wild type (WT) mice. However, glucose loading (2 g/kg) rendered the β2 KO mice significantly more glycemic during the following 120 min compared to WT mice (Fig.2A).

**In vitro insulin secretion.** The ablation of β2 AR receptor by siRNA (called 1972) in INS-1E is sufficient to inhibit both glucose and sulphonylureas (glyburide) stimulated insulin secretion, (Fig.5A). Interestingly, a specific β2AR blocker, ICI 118551, was able to impair glucose stimulated insulin secretion whilst fenoterol, a specific β2AR agonist, significantly increase the insulin secretory response to glucose in INS-1E cells (Fig.5B).

**Involvement of Pparγ.** We have evaluated the expression levels of PPARγ mRNA in INS-1E cells treated with specific β2AR agonists or antagonists to modulate β2AR function. Pparg expression levels increased with β2AR agonist fenoterol whilst β2AR blocker ICI 118551, decreased Pparg mRNA levels (Fig.5A). ICI reduced capability of INS-1E to secrete insulin after glucose stimulation. However the secretion was restored, when cells were transfected with cDNA encoding PPARγ (Fig.5B). Collectively, this findings supports a key role of Pparγ in the regulation of beta-cell functions by β2AR.

**Hypothesis:** We hypothesize that the loss of β2AR at pancreatic level causes a reduction in Pparg expression and PDX1 activation. This could be the underlying mechanism for the impaired insulin secretion in mice lacking β2AR.4,6,7

**Conclusion:**
β2AR plays a critical role in glucose metabolism by affecting insulin secretion through a mechanism involving Pparg and Pdx-1.

**Essential References**
2. Firth BM et al., Endocrinology 2010; 151: 2036-2043.

**References**
- Firth BM et al., Endocrinology 2010; 151: 2036-2043.
- Trapani R et al., Diabetes Res 2010; 90(2): 132-141.