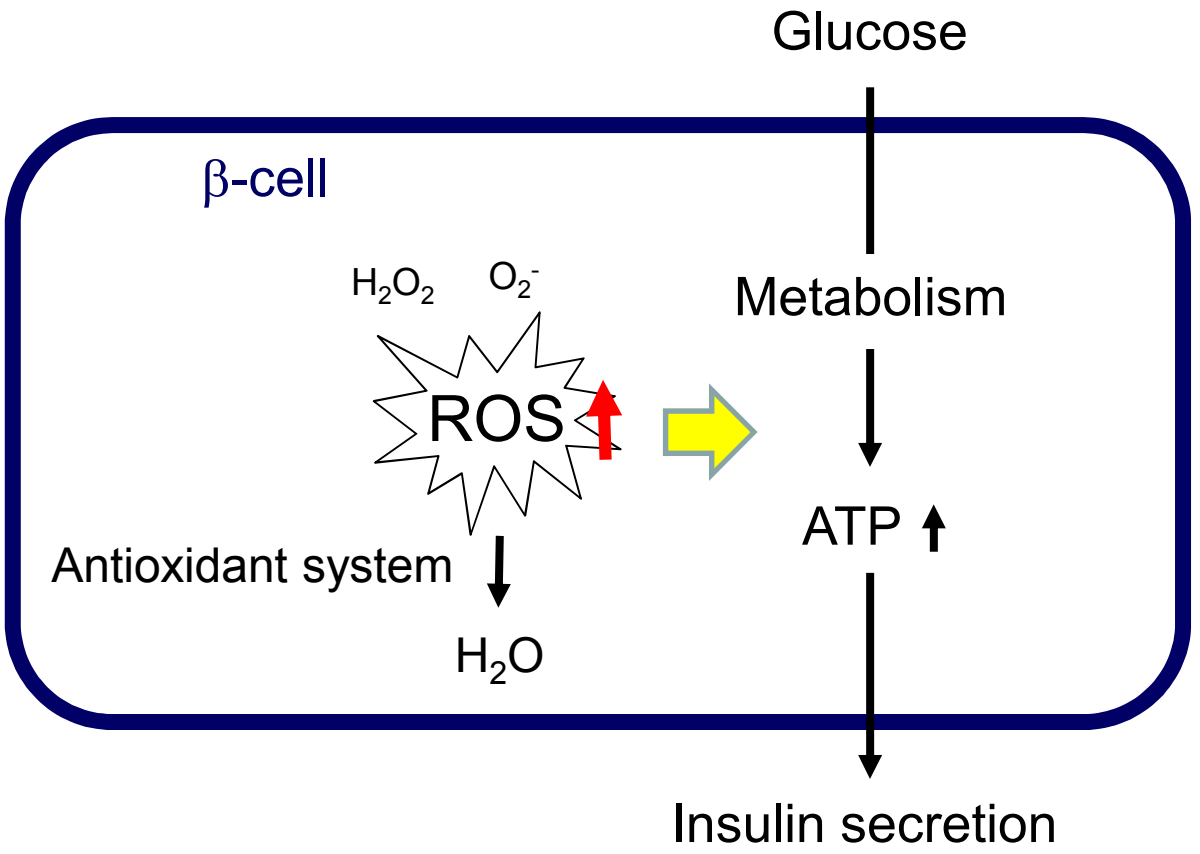
Role of endogenous ROS in pancreatic β-cell dysfunction

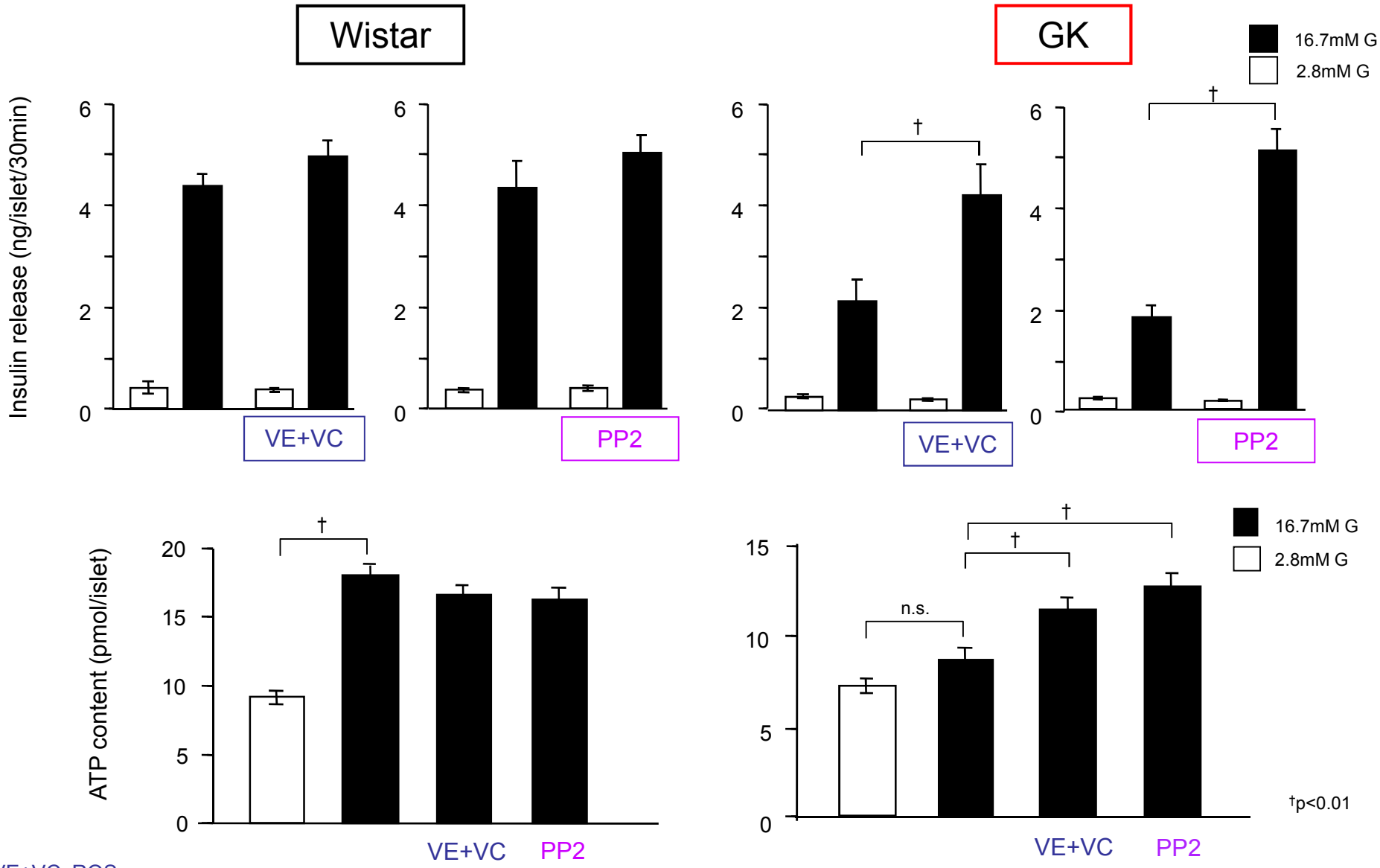
Chiba University Graduate School of Medicine

Eri Mukai

The effect of endogenous ROS on metabolism-secretion coupling



Src inhibition ameliorates impaired IS and ATP production in GK islets

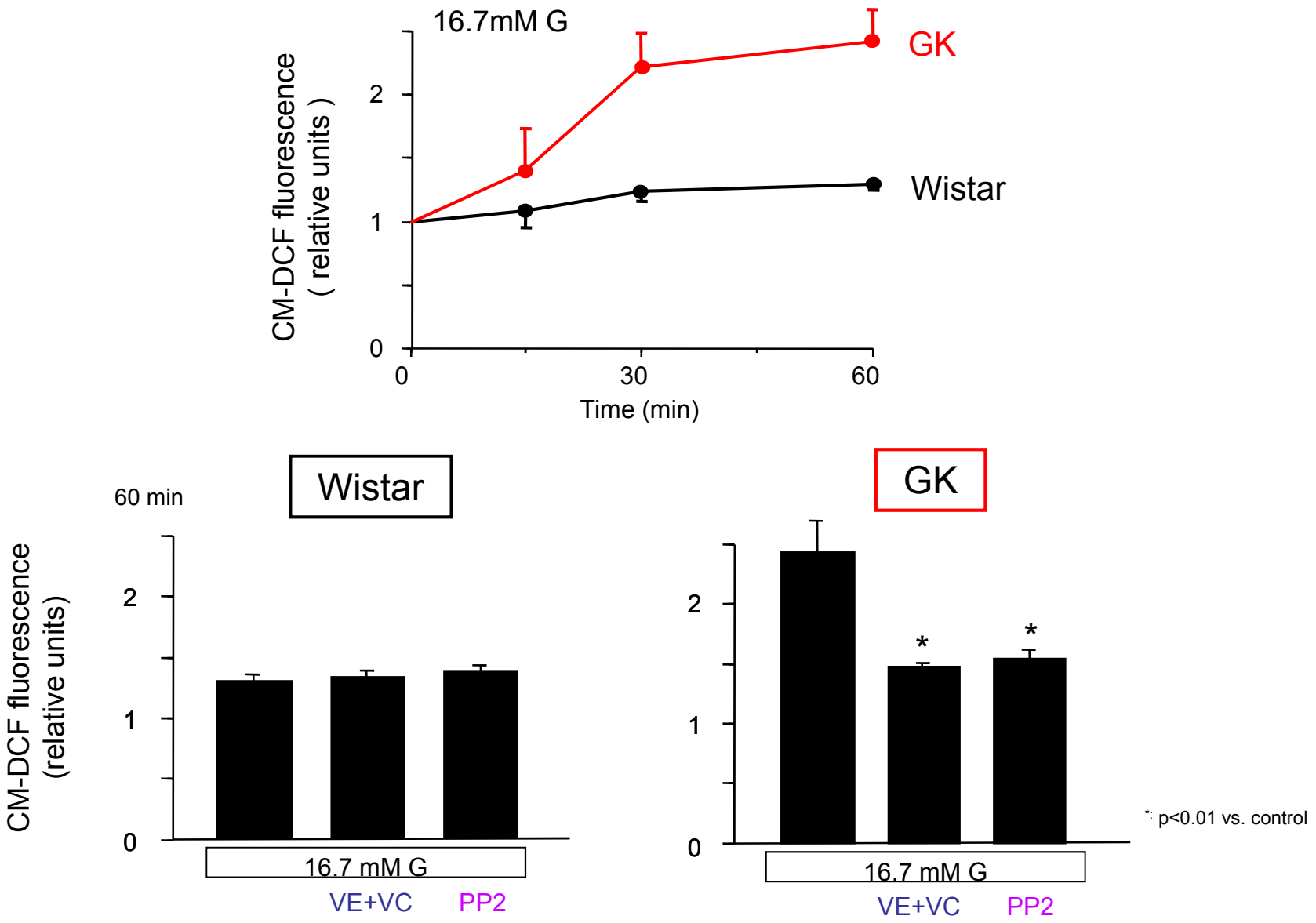


VE+VC: ROS scavenger

PP2 (10 μM): Src inhibitor

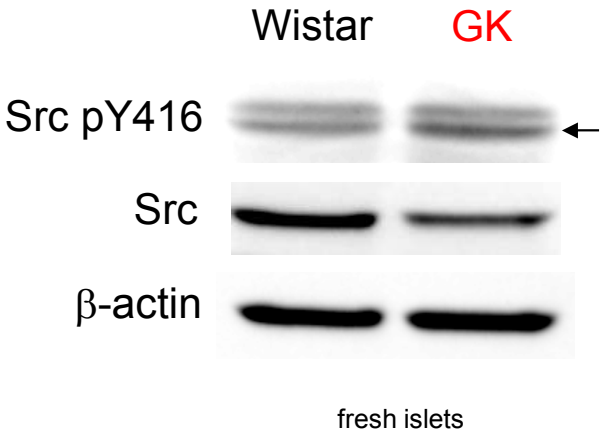
Kominato R, et al. Diabetologia, 2008

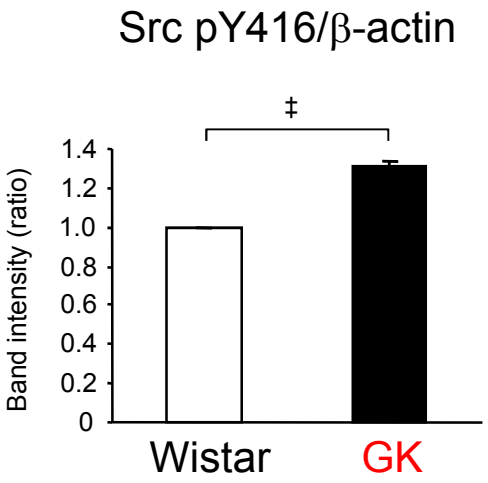
Src inhibition decreases ROS production in GK islet cells

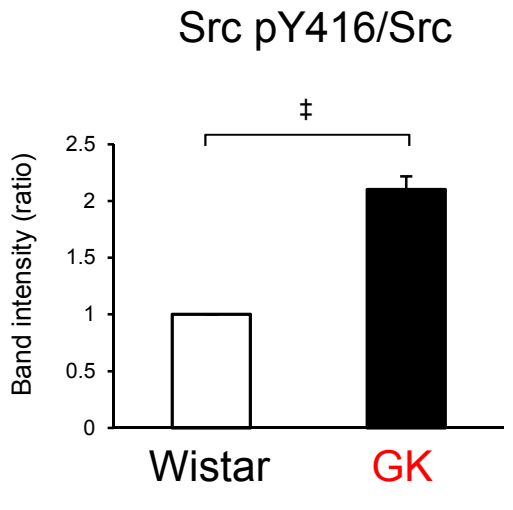


Kominato R, et al. Diabetologia, 2008

Src activity is endogenously up-regulated in GK islets





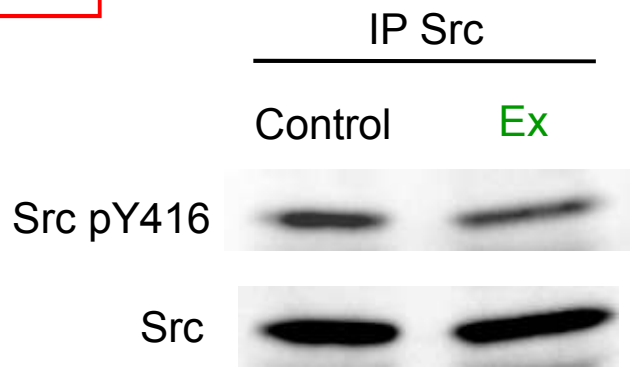


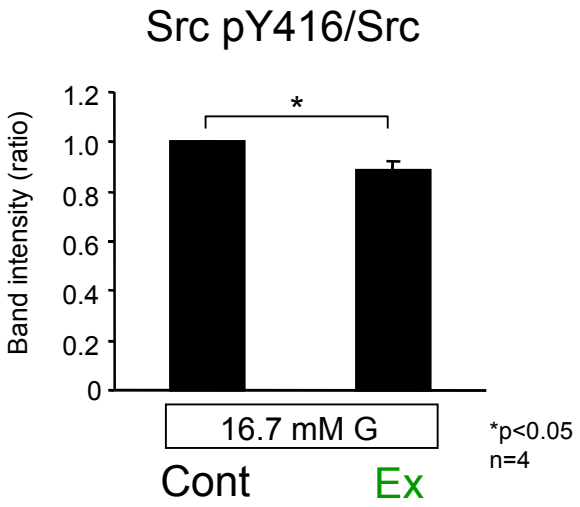
†p<0.01
‡p<0.001
n=3

Mukai E et al. Diabetes, 2011

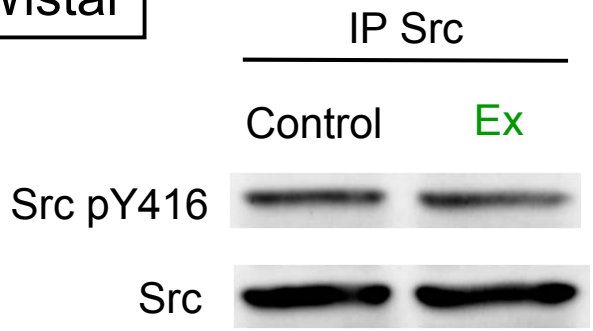
Exendin-4 suppresses Src activity in GK islets

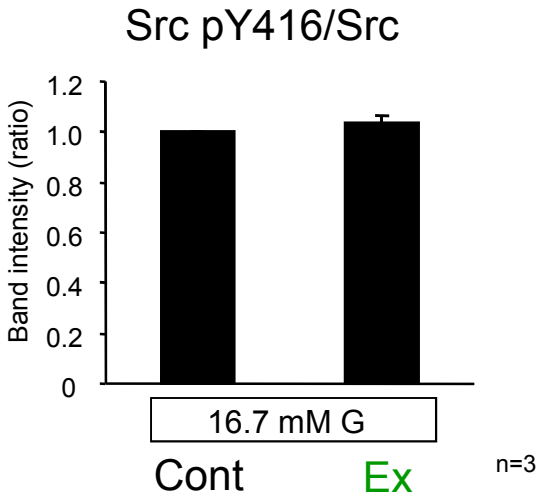
GK





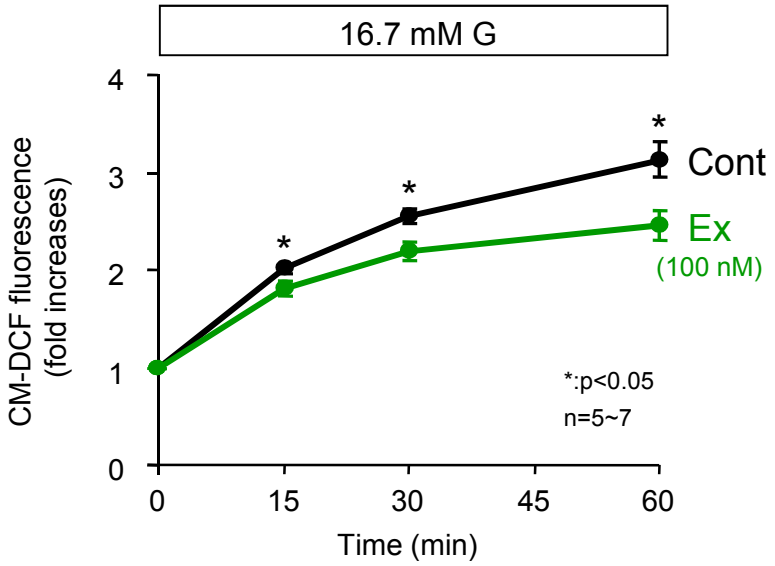
Wistar

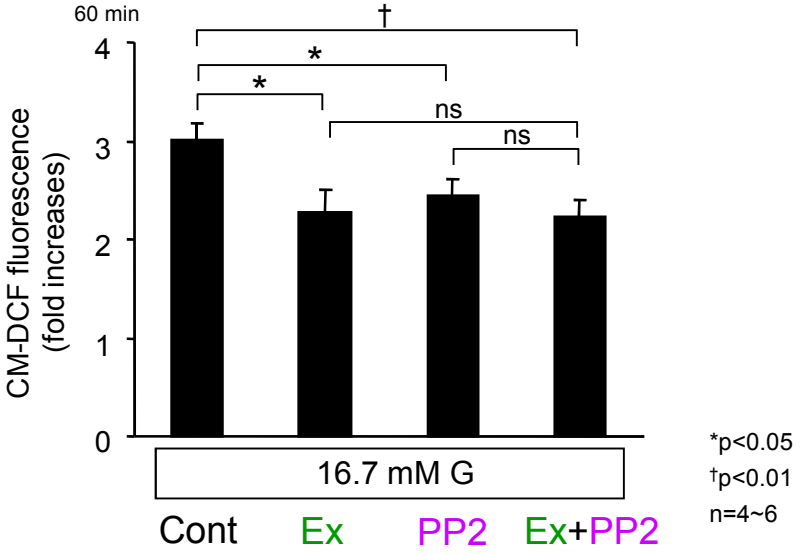




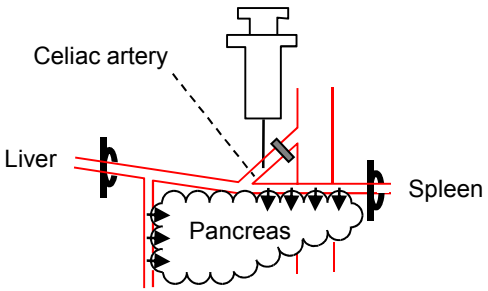
Mukai E et al. Diabetes, 2011

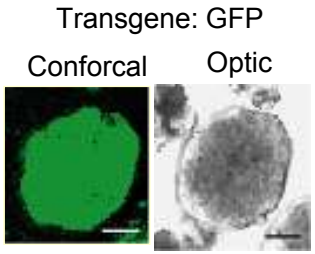
Exendin-4 decreases ROS production in GK islet cells



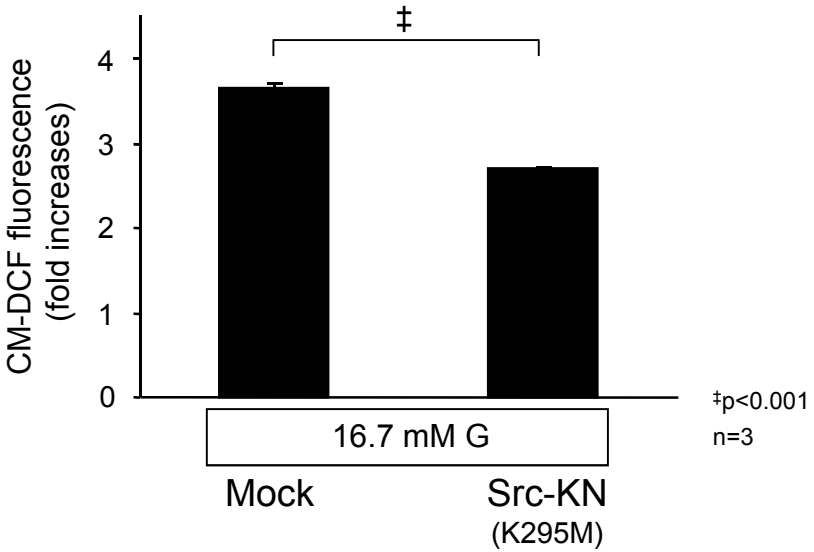


in vivo gene transfection



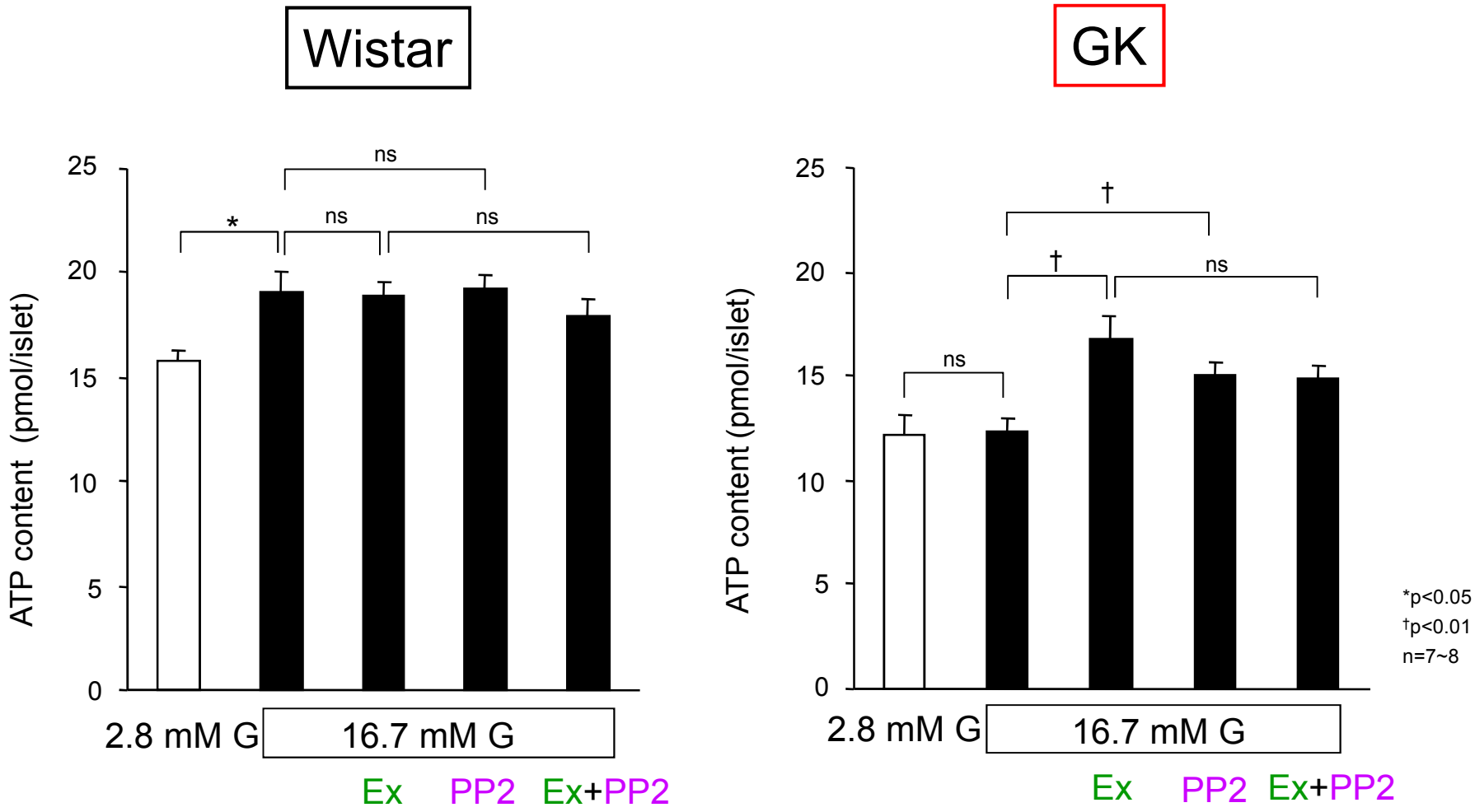


Mukai E, et al. J. Cont. Res., 2007.



Mukai E et al. Diabetes, 2011

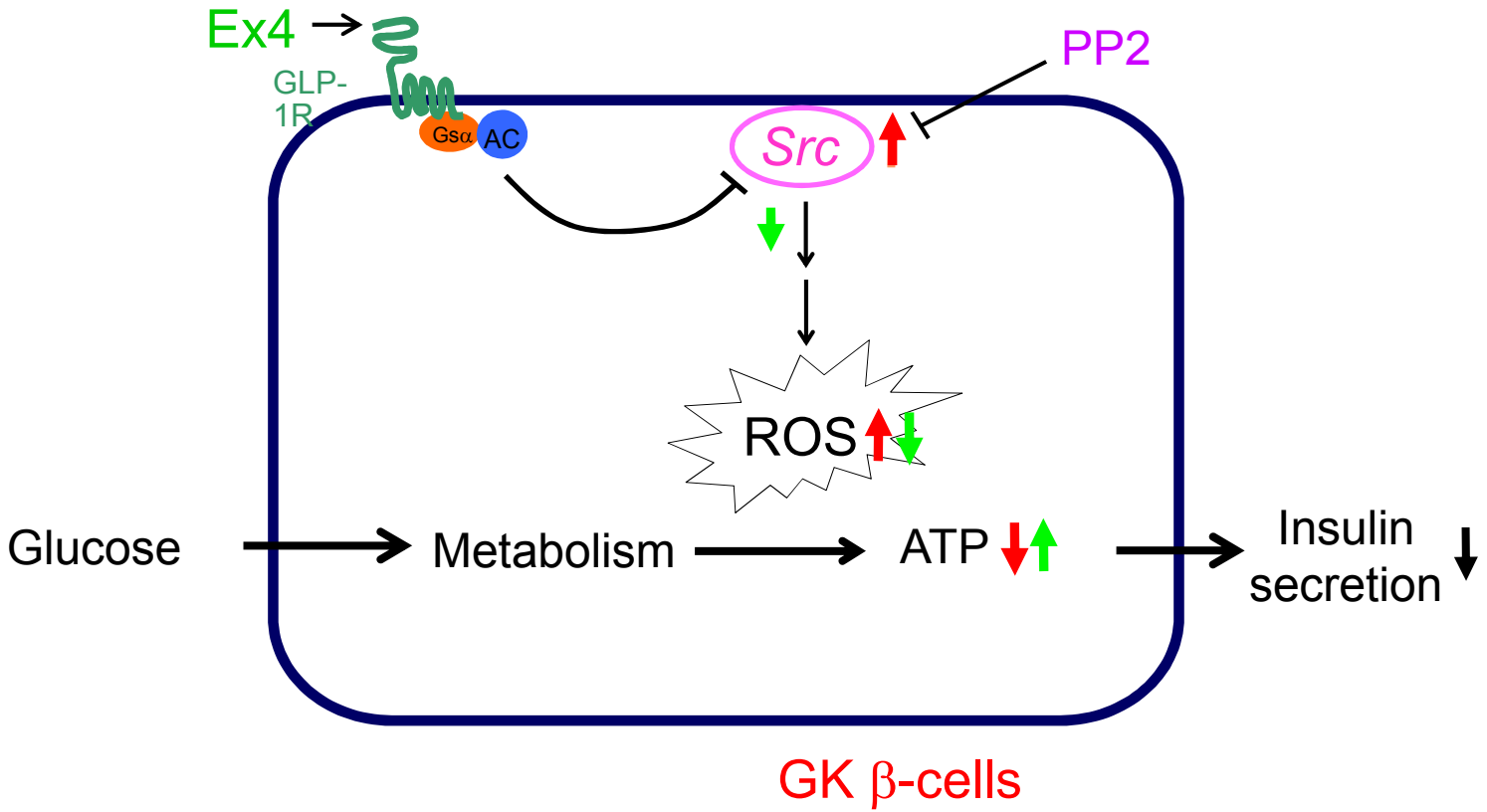
Exendin-4 increases ATP production in GK islets



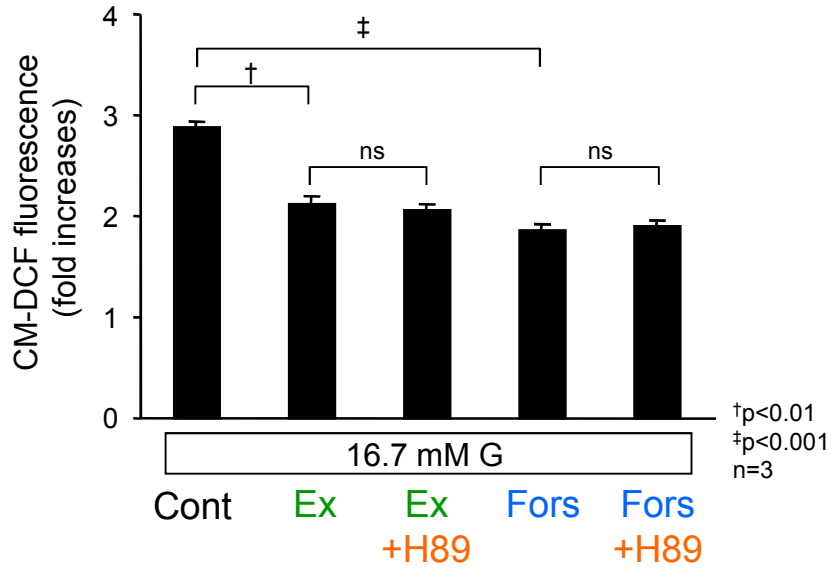
Mukai E et al. Diabetes, 2011

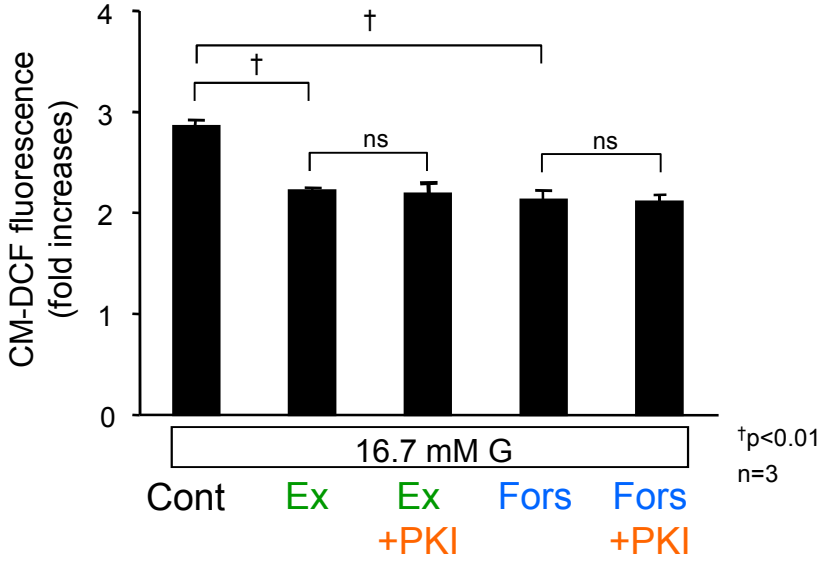
Summary 1

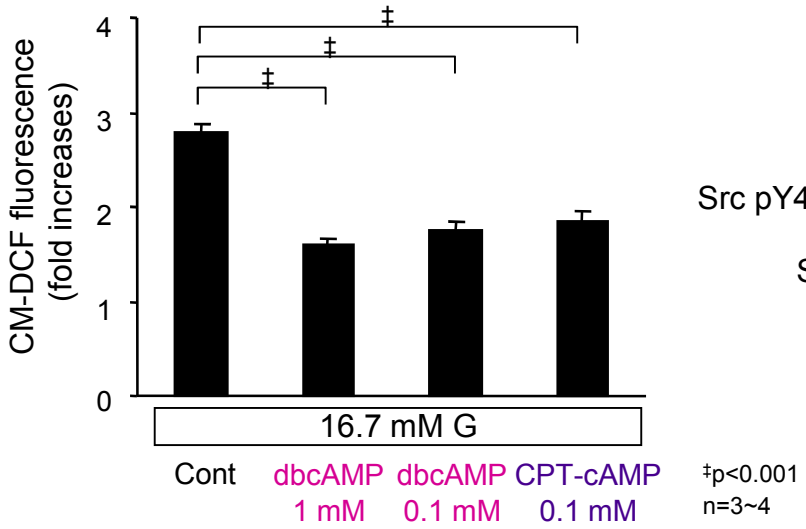
Src activity is endogenously up-regulated in GK islets, which contributes to ROS production and impaired ATP production.
GLP-1 signal ameliorates ROS production and ATP production through suppression of Src activation.

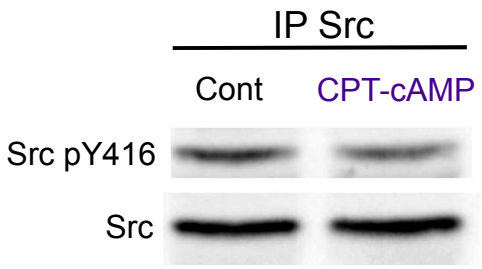


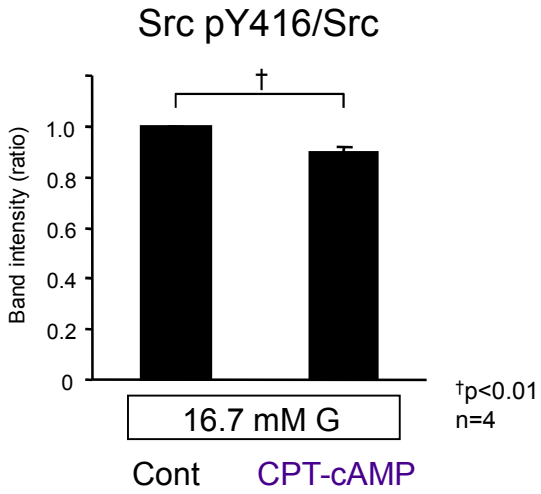
The decrease in ROS production by exendin-4 is dependent on Epac





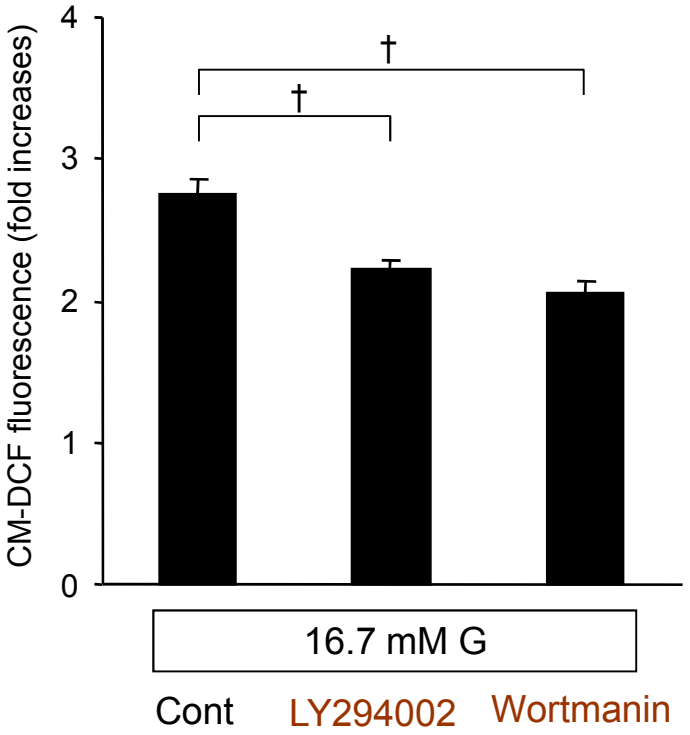






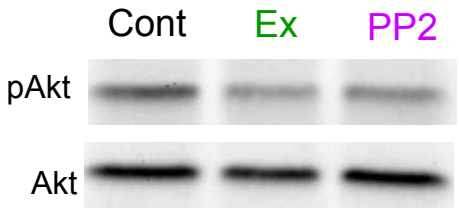
Mukai E et al. Diabetes, 2011

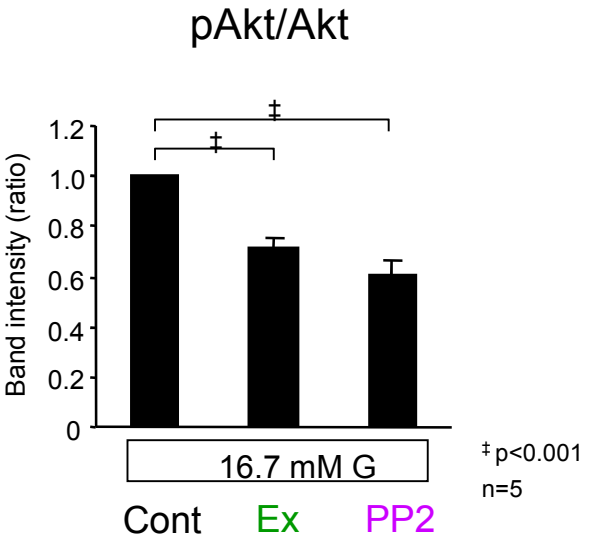
PI3-K/Akt signaling is involved in the downstream pathway of Src



†p<0.01
n=3~4

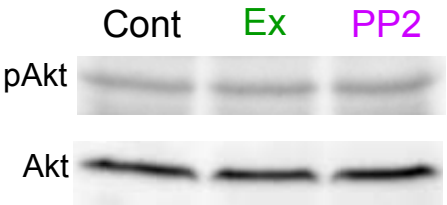
GK

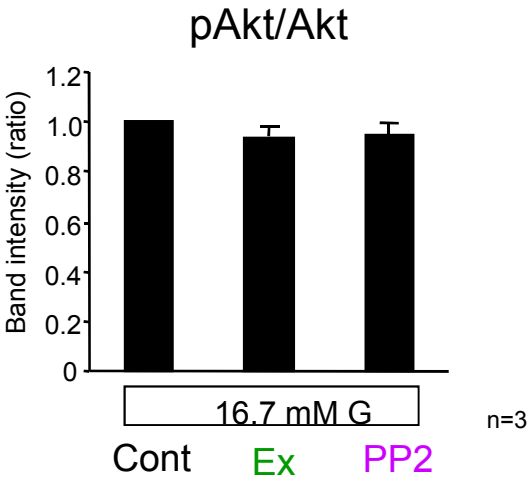




‡p<0.001
n=5

Wistar





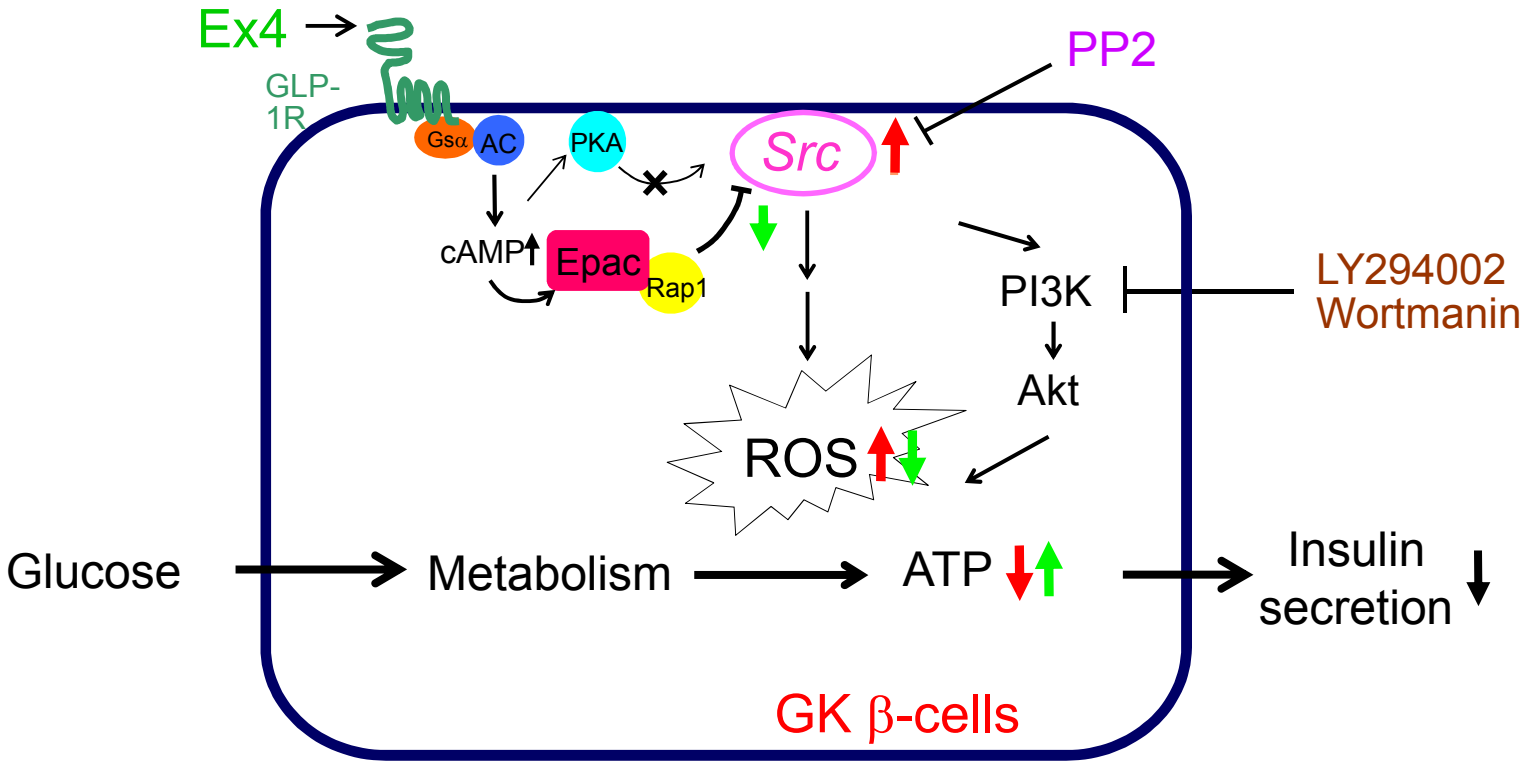
n=3

LY294002 (50μM), Wortmanin (0.5μM): PI3-K inhibitor

Mukai E et al. Diabetes, 2011

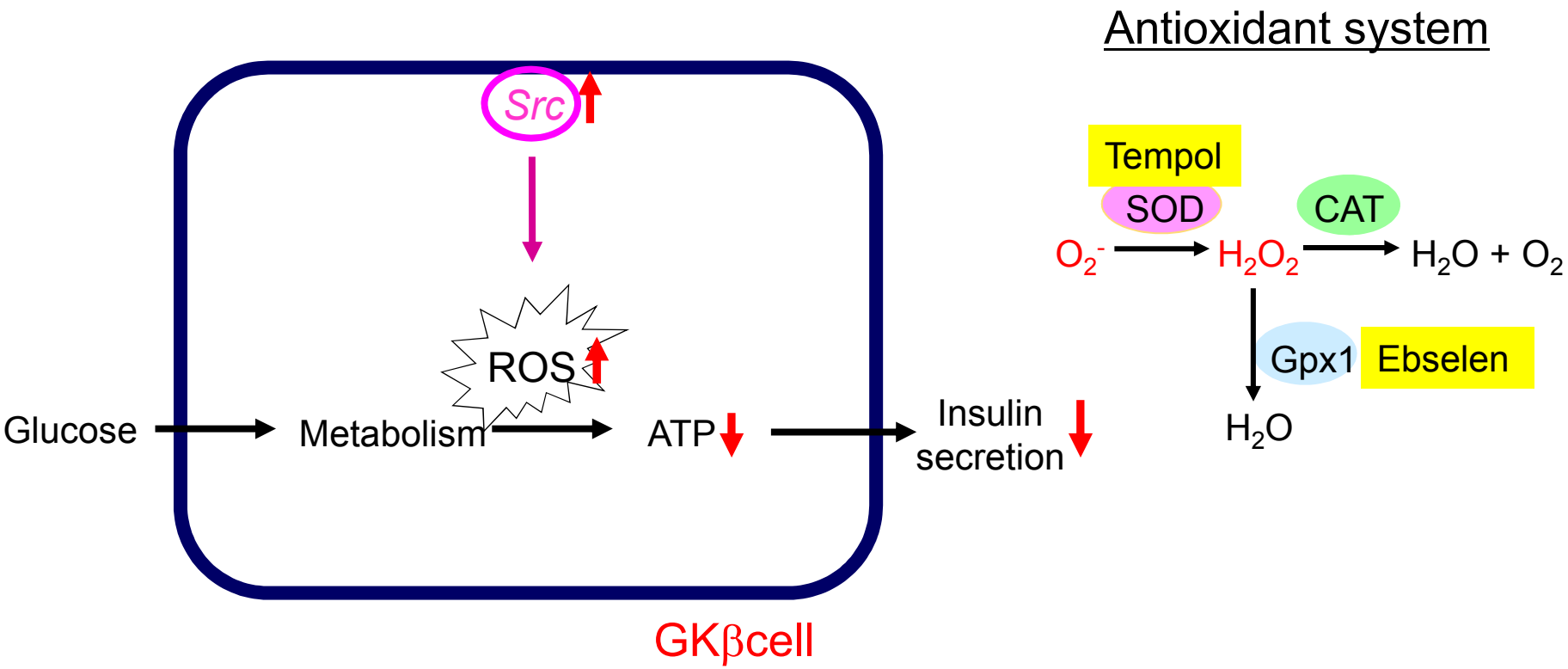
Summary 2

The effects of exendin-4, suppression of Src activity and decrease in ROS production, are dependent on not PKA but Epac.
PI3K/Akt signaling, inhibited by exendin-4 or Src inhibitor, is involved in the downstream pathway of Src and regulates ROS production.

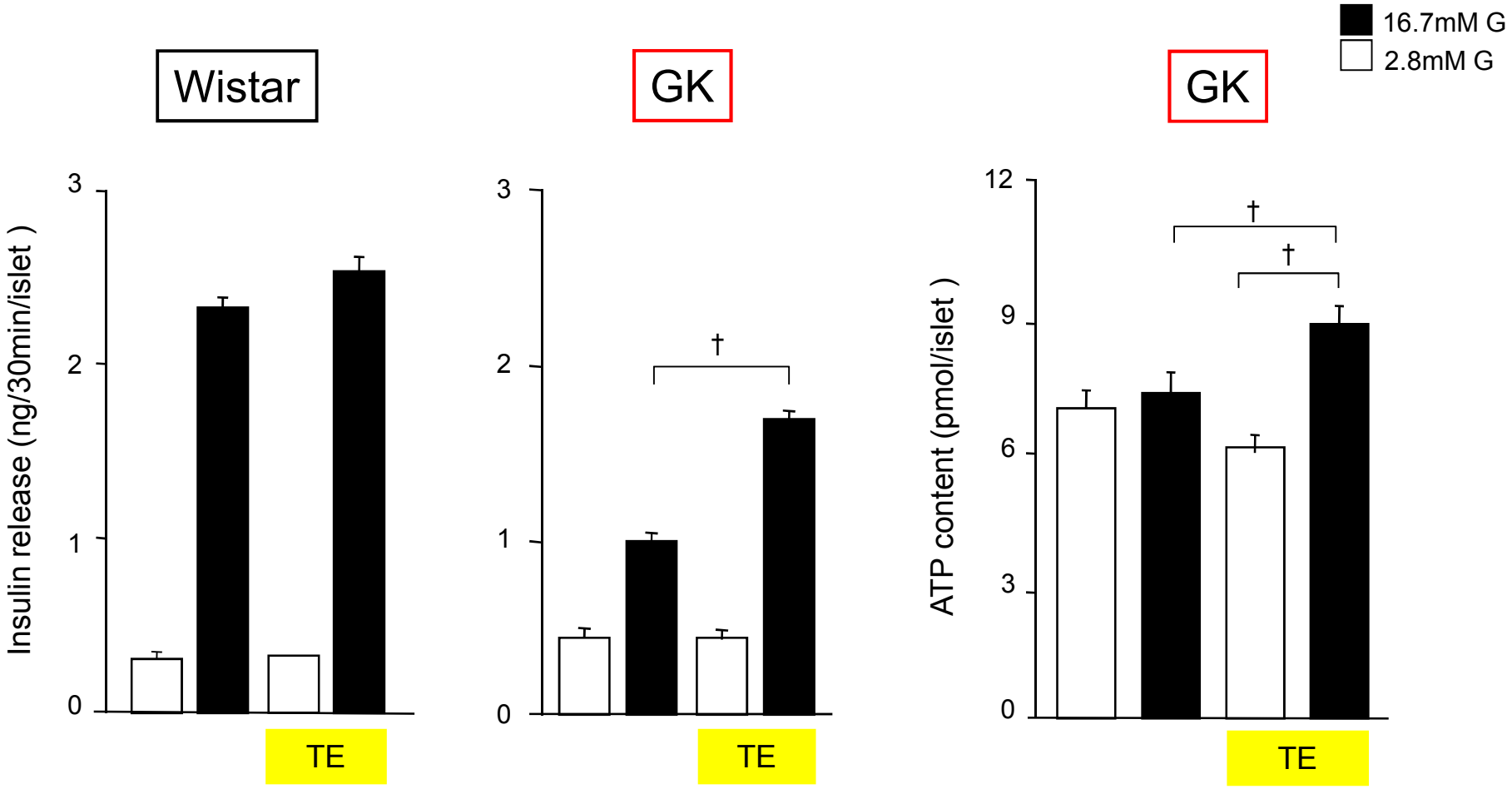


GLP-1 signaling improve β-cell function in the diabetic state because it ameliorates impaired metabolism-secretion coupling

The effect of a longer suppression of ROS on metabolism-secretion coupling



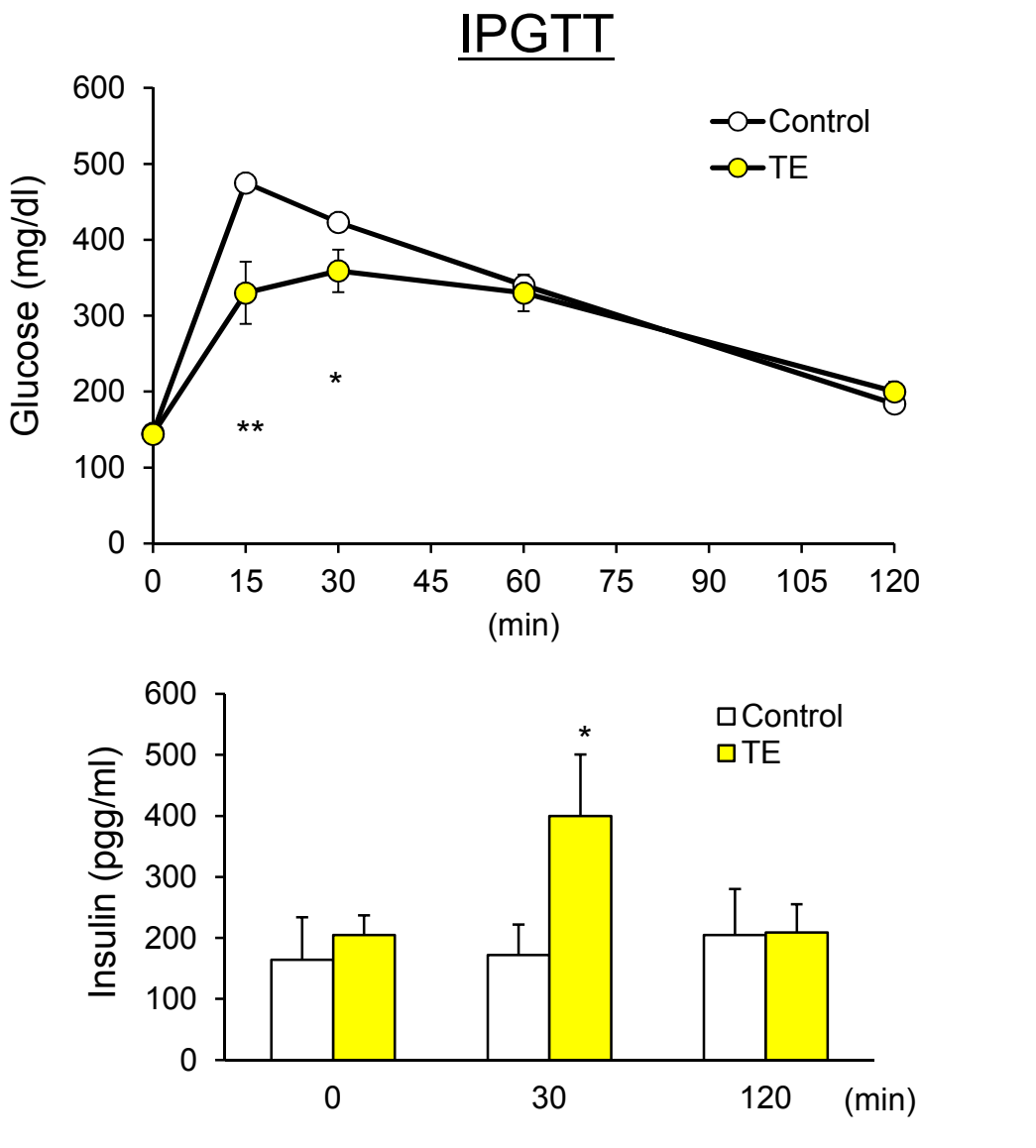
TE treatment ameliorates impaired IS and ATP production in GK islets



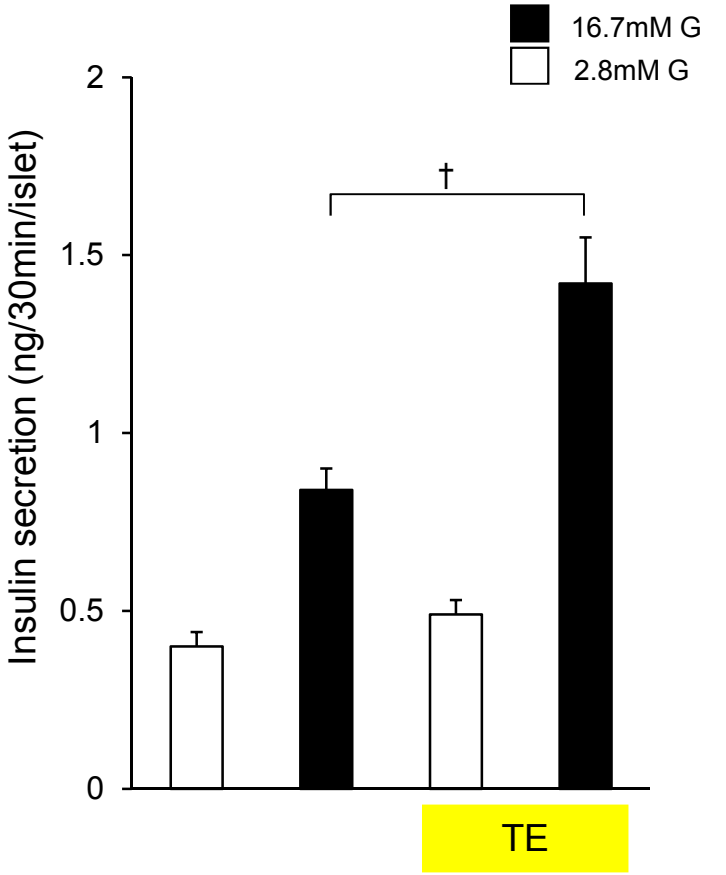
†p<0.01

Sasaki M et al. Diabetes, 2013

The effect of *in vivo* TE treatment on β-cell function in GK



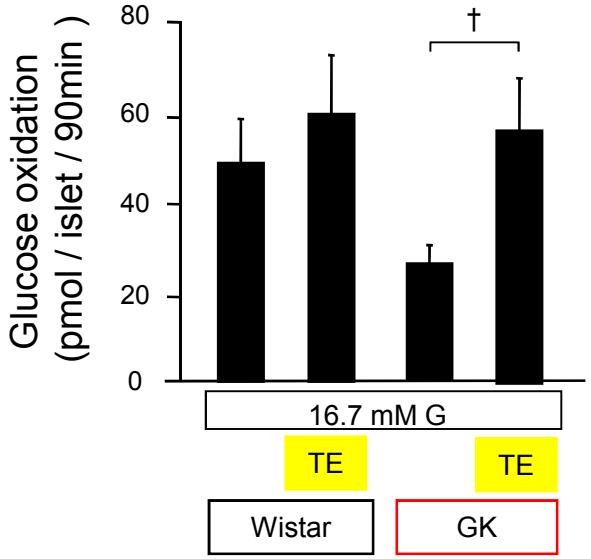
*p<0.05, **p<0.01 vs control

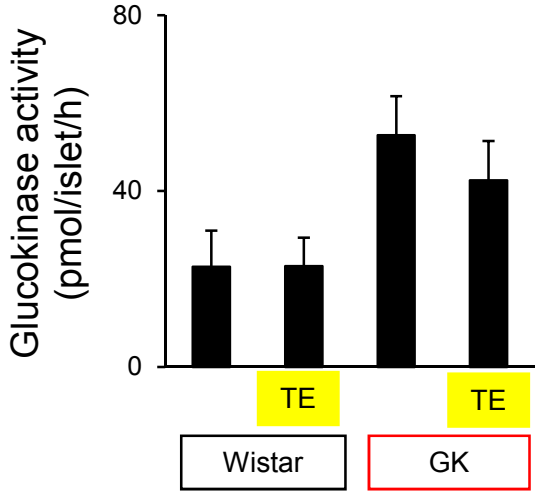


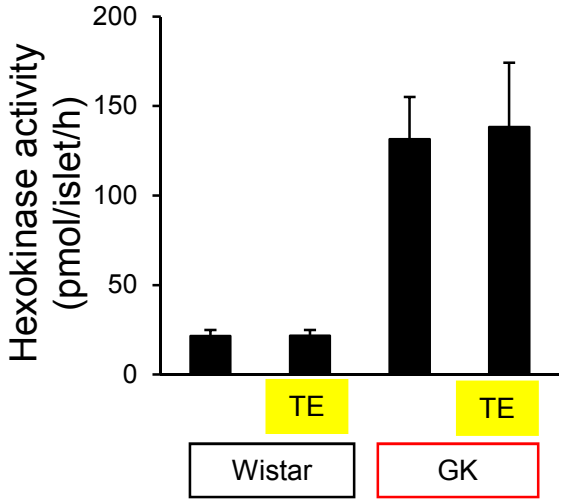
*p<0.01 vs control

Sasaki M et al. Diabetes, 2013

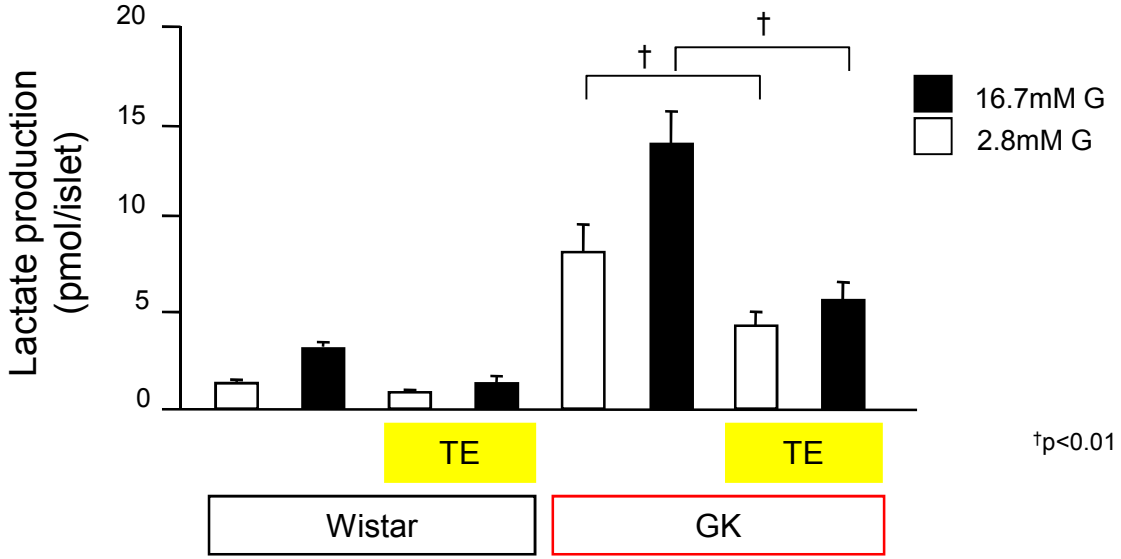
Lactate overproduction uncouples between glycolysis and mitochondrial oxidation in GK islets





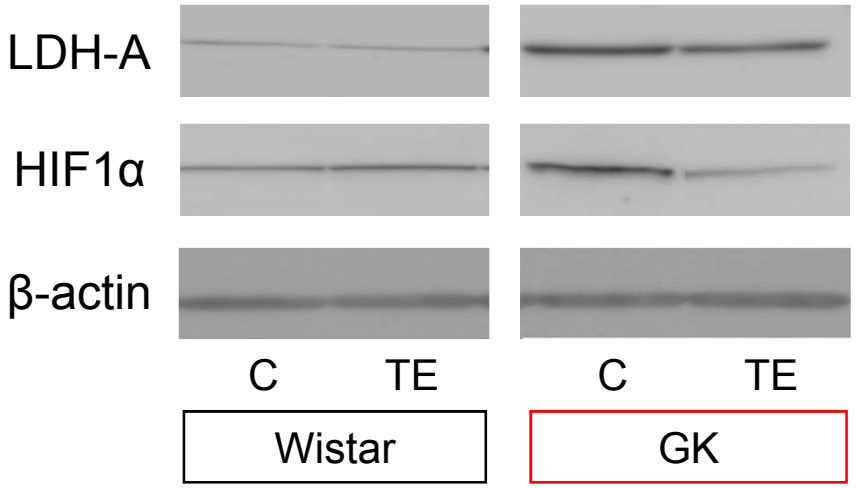


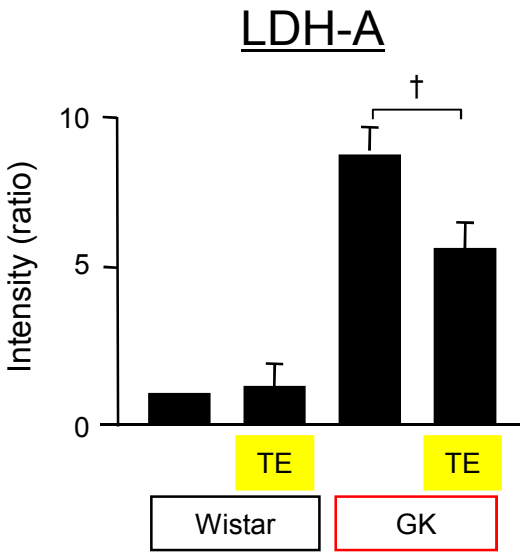
Glucose
↓ Glycolysis
Pyruvate → Lactate
↓ Oxidation
Krebs cylcle

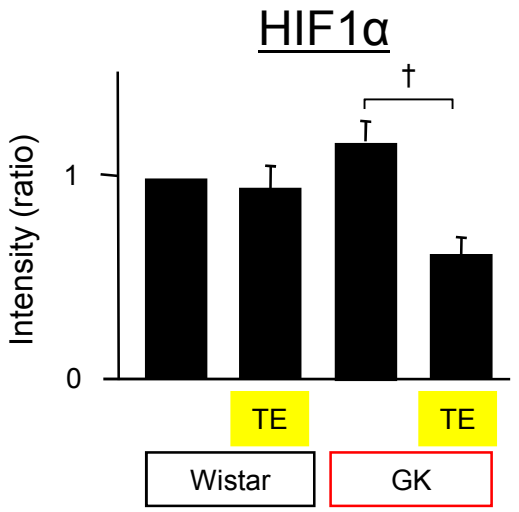


Sasaki M et al. Diabetes, 2013

TE treatment decreases the expression levels of LDH-A and HIF1α in GK islets



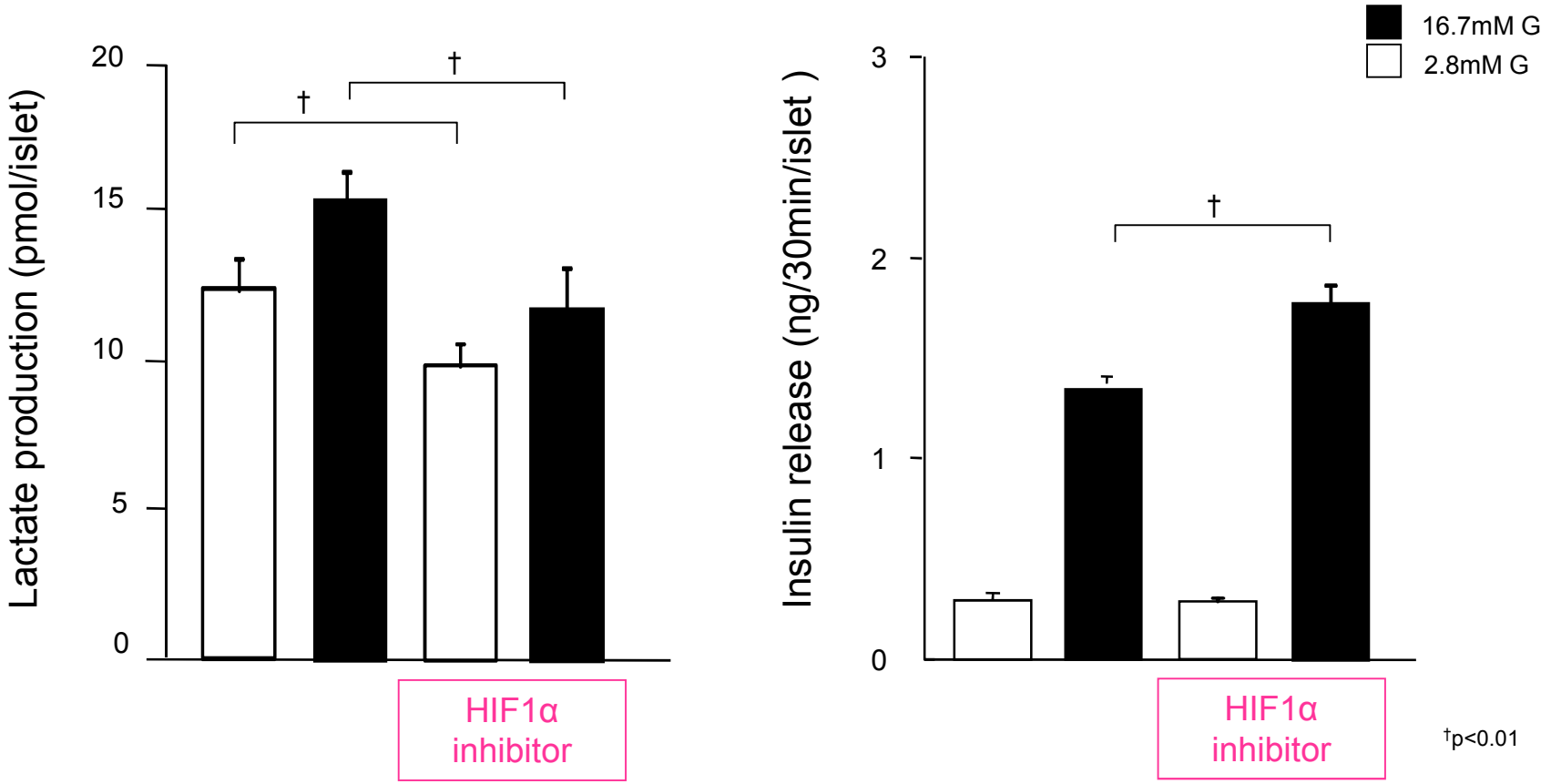




†p<0.01

Sasaki M et al. Diabetes, 2013

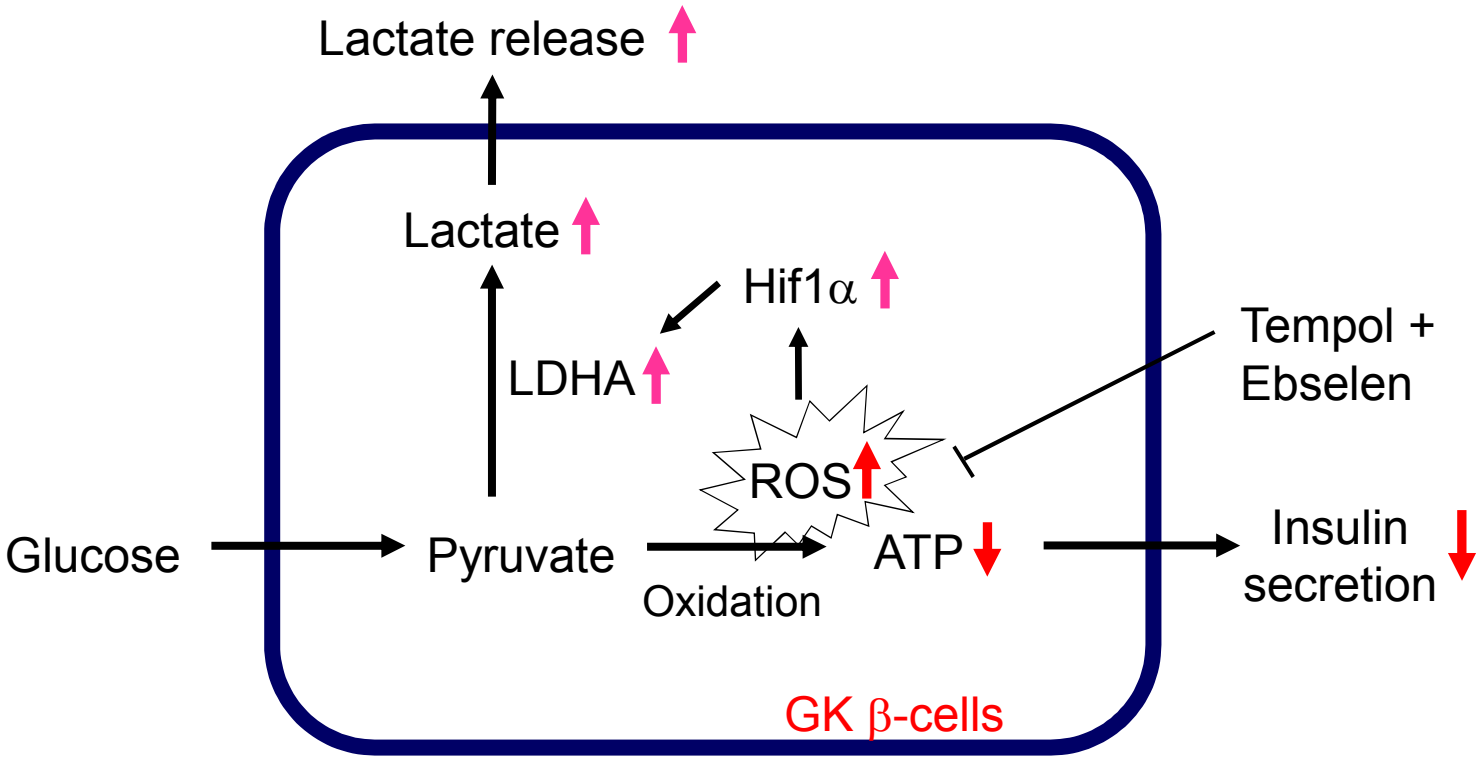
HIF1α inhibition improves lactare overproduction and IS in GK islets



Sasaki M et al. Diabetes, 2013

Summary 3

ROS reduction ameliorates metabolism-secretion coupling by suppressing lactate overproduction through the inhibition of HIF1α stabilization.
The Warburg-like effect, which is characteristic of aerobic metabolism in cancer cells by which lactate is overproduced with reduced linking to mitochondrial metabolism, plays an important role in impaired metabolism-secretion coupling in diabetic β-cells.



Acknowledgments

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