Defects in glucose utilization & GLP-1

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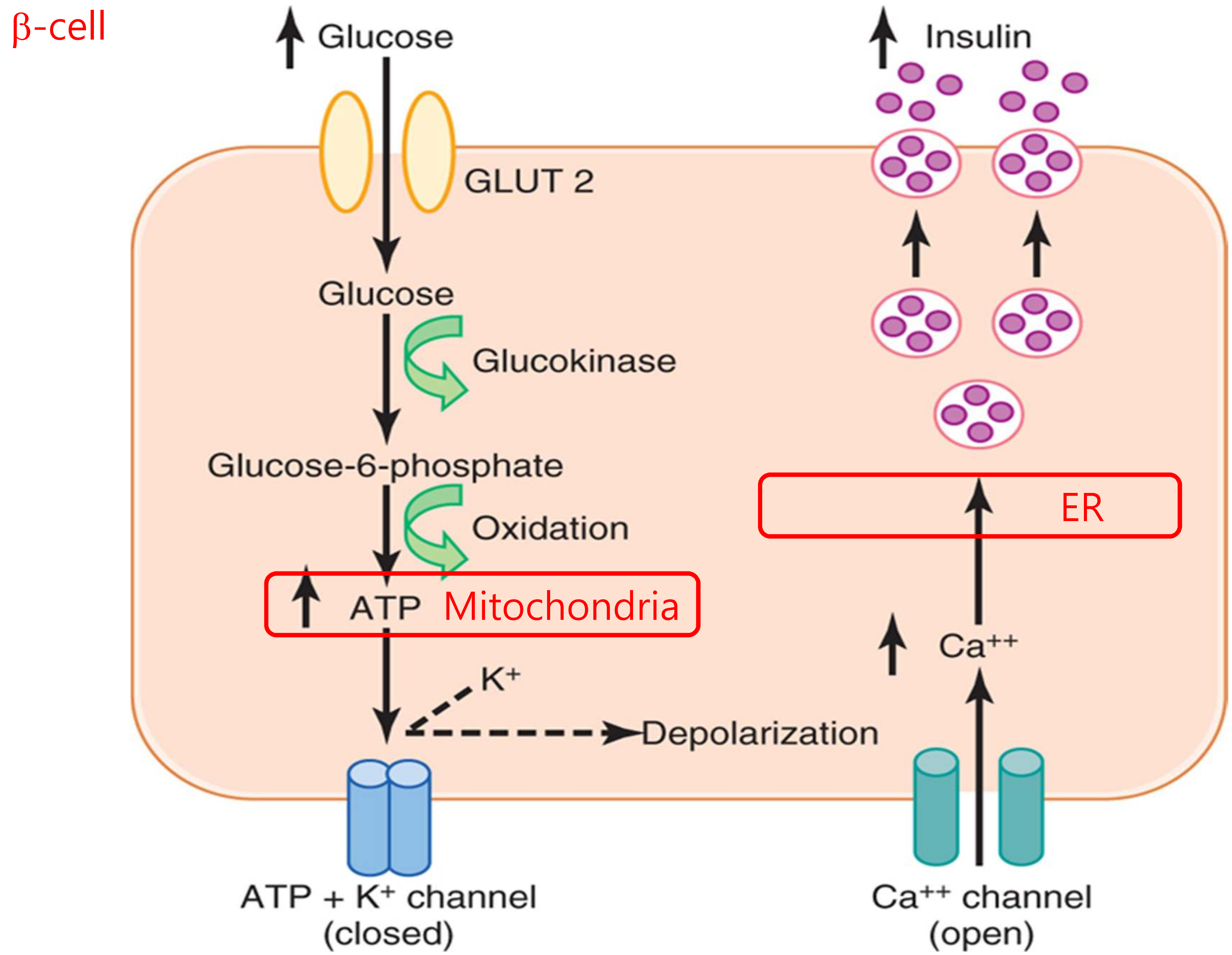
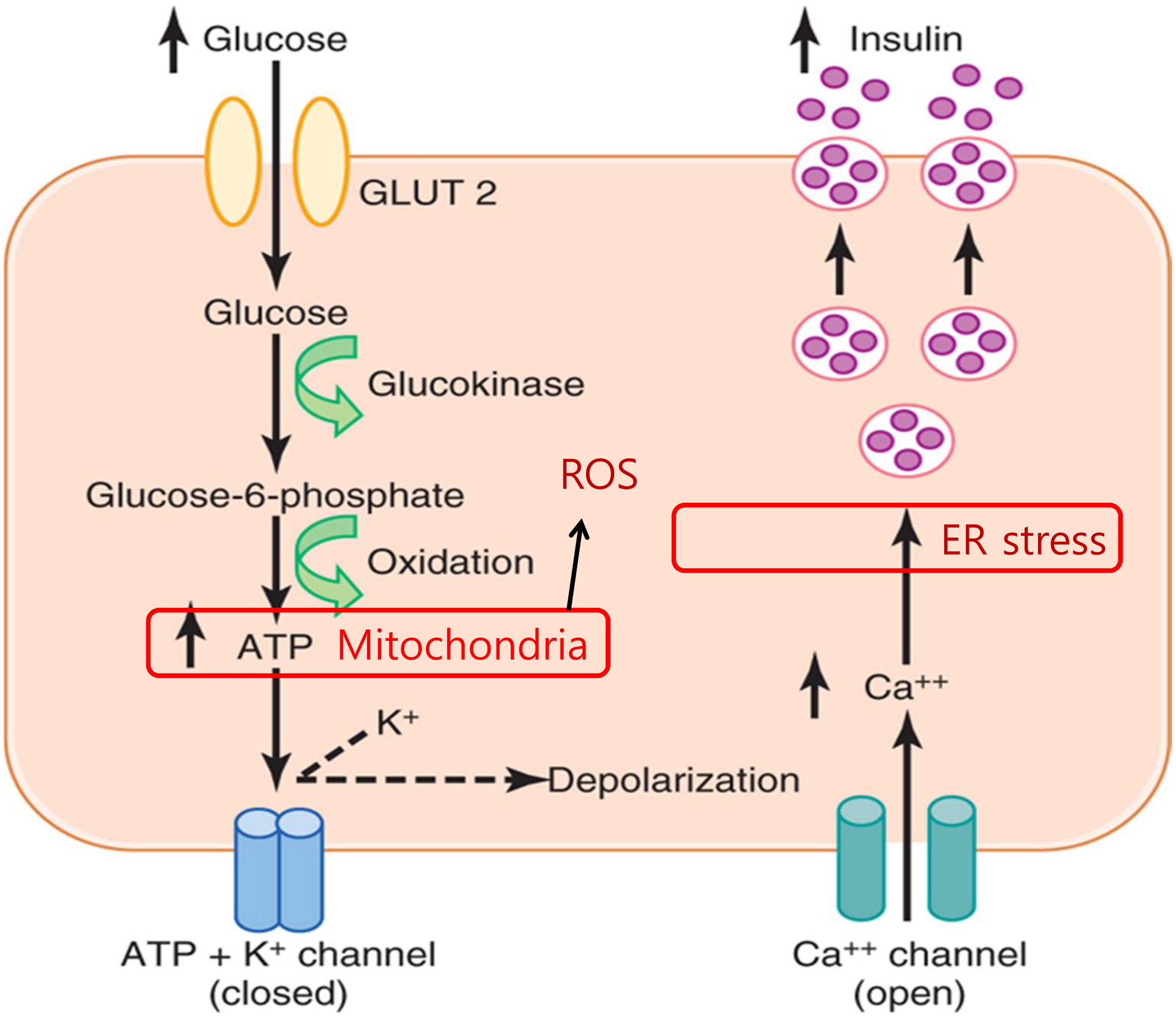
High glucose in normal person



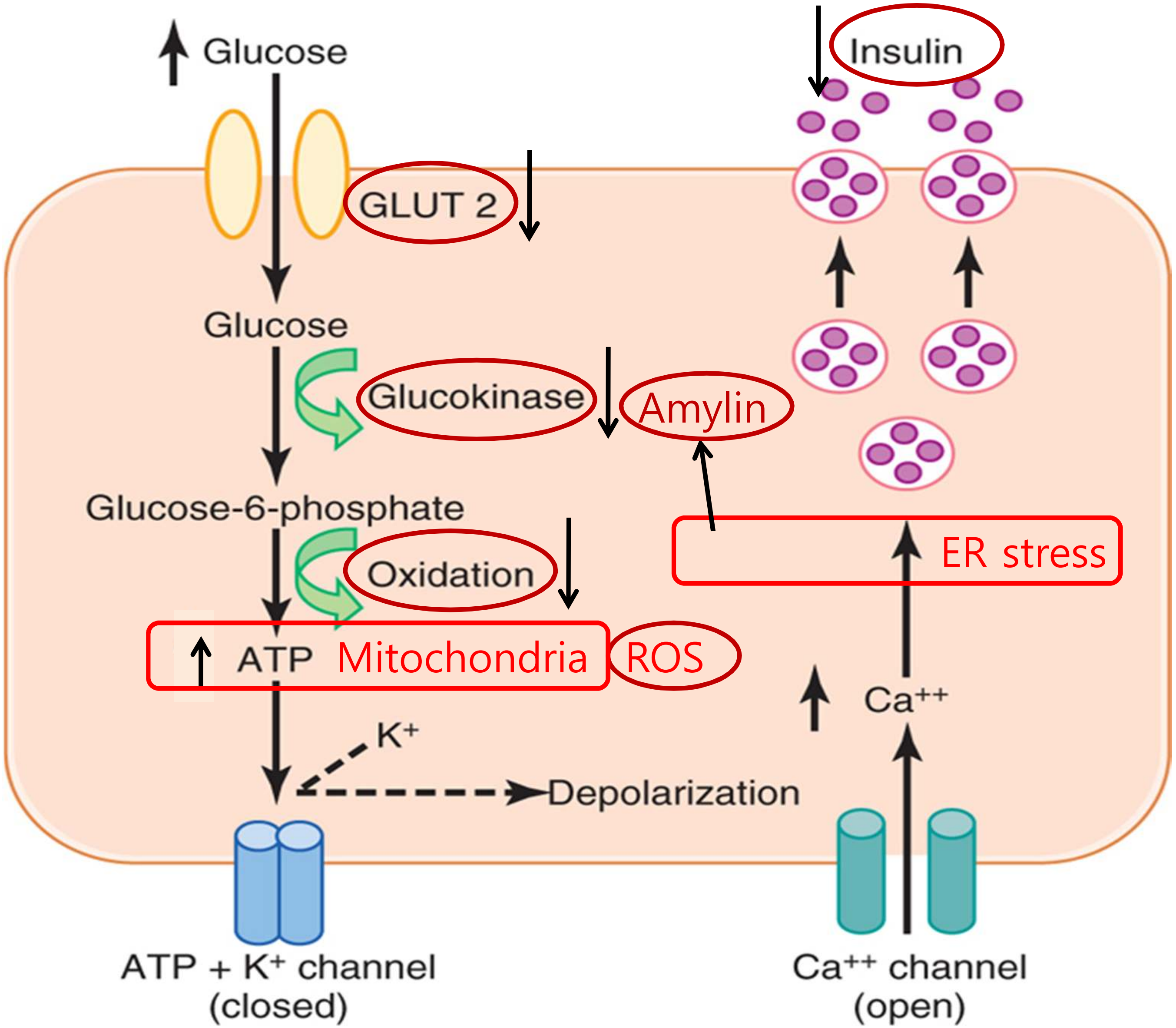
High glucose in prediabetes

β-cell



High glucose in diabetes

β-cell



High glucose in diabetes

↓

- β-cell death

Surviving β-cell

- Impaired glucose-stimulated insulin secretion

↓

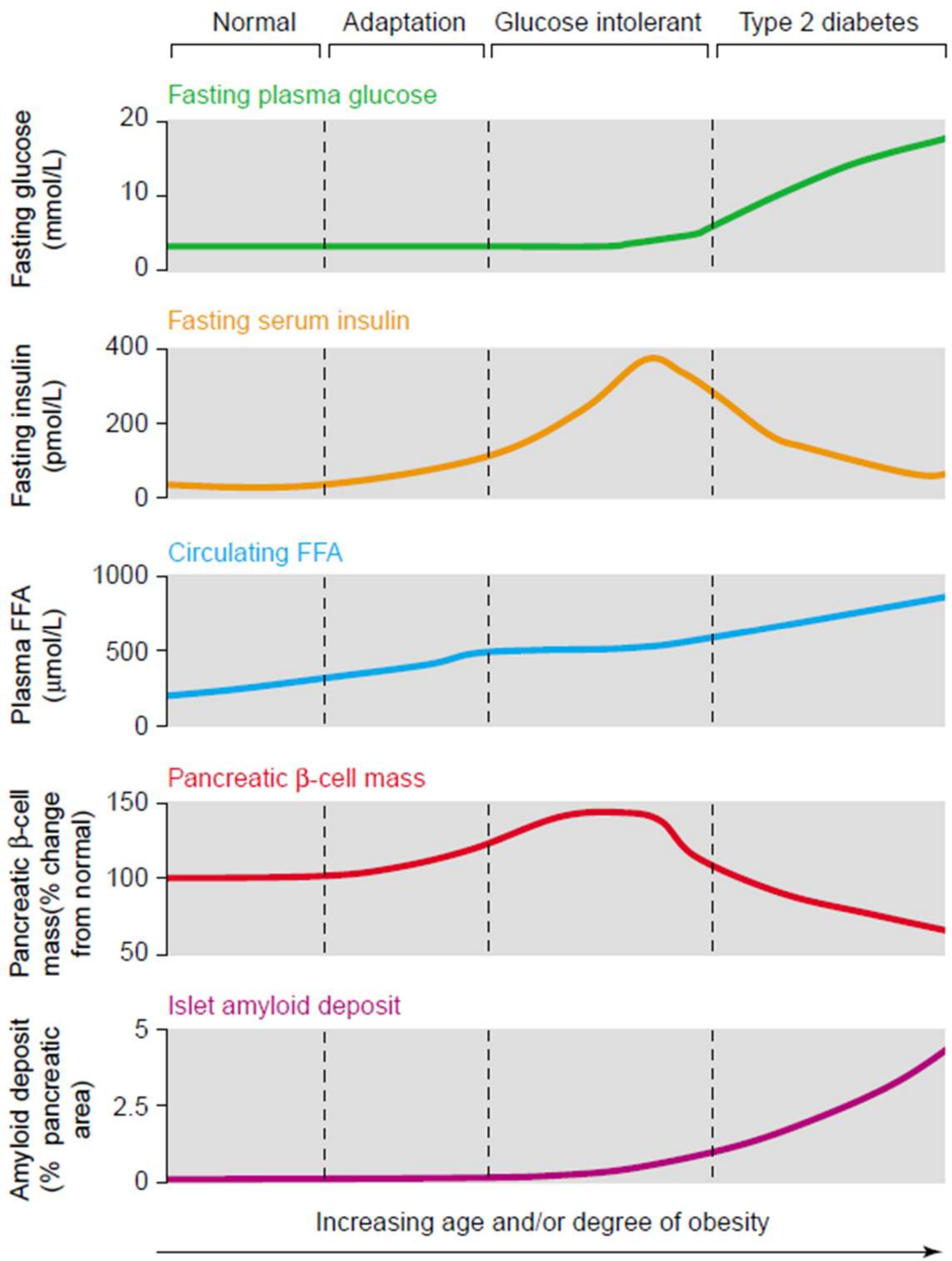
- Insufficient amount of insulin in the blood (vs. glucose)
- Decreased negative feedback toward glucagon secretion

↓ ***Low I/G ratio***

- Impaired glucose utilization in insulin-sensitive tissues
- Glucose toxicity in various tissues

↓

Diabetic complications



Normal
Adaptation
Glucose intolerant
Type 2 diabetes
Fasting plasma glucose
Fasting glucose (mmol/L)
20
10
0
Fasting serum insulin
Fasting insulin (pmol/L)
400
200
0
Circulating FFA
Plasma FFA (µmol/L)
1000
500
0
Pancreatic β-cell mass
Pancreatic β-cell mass(% change from normal)
150
100
50
Islet amyloid deposit
Amyloid deposit (% pancreatic area)
5
2.5
0
Increasing age and/or degree of obesity

Brain in diabetes

Neurons rely on glucose metabolism for function and survival

[Biessels GJ et al, Eur J Pharmacol, 2004]

Neurodegenerative disorders: impairments in the glucose availability

[Adhihetty PJ & Beal MF, Neuromol Med, 2008]
[Browne SE et al, Neurobiol Dis, 2006]

: Parkinson's disease, Huntington's disease, Alzheimer's disease, Amyotrophic lateral sclerosis

↓

Neurotransmitter release defects by low ATP
AMPK-mediated, ER stress-mediated cell death
In diabetes, glucose availability much lower

↓

Exaggeration of the diseases

<u>Glucagon-like peptide-1</u>

↓

In diabetic β-cells,

Unlike gastric inhibitory peptide (GIP)

- Acute effect

Potentiated glucose-dependent insulin secretion → glucagon↓

- Chronic effects

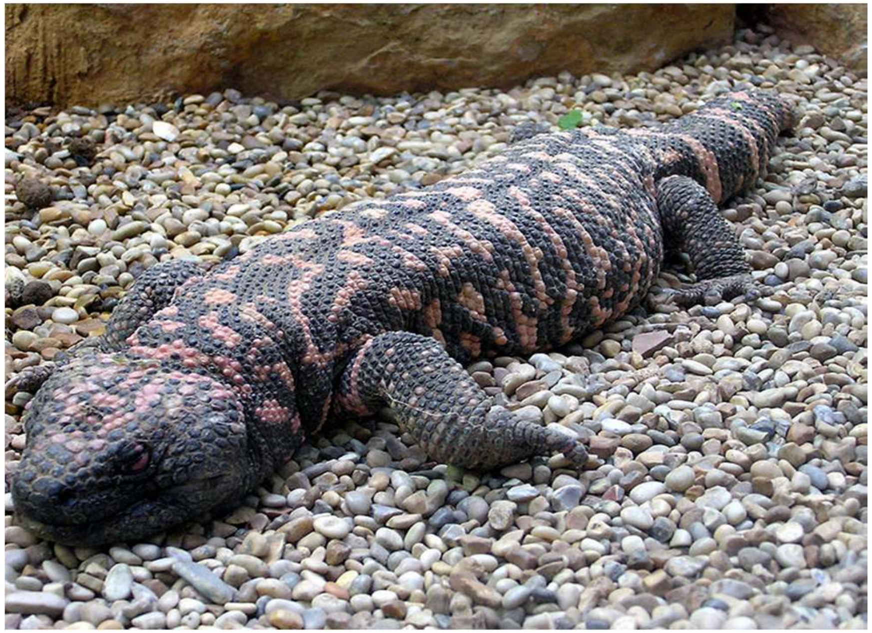
Increased insulin gene expression & biosynthesis
Decreased apoptosis
Increased proliferation and neogenesis (in animal experiments)

↓ ***High I/G ratio***

Appetite↓ → *Lowers blood glucose levels in human DM* ← GI motility↓

GLP-1 synthesis

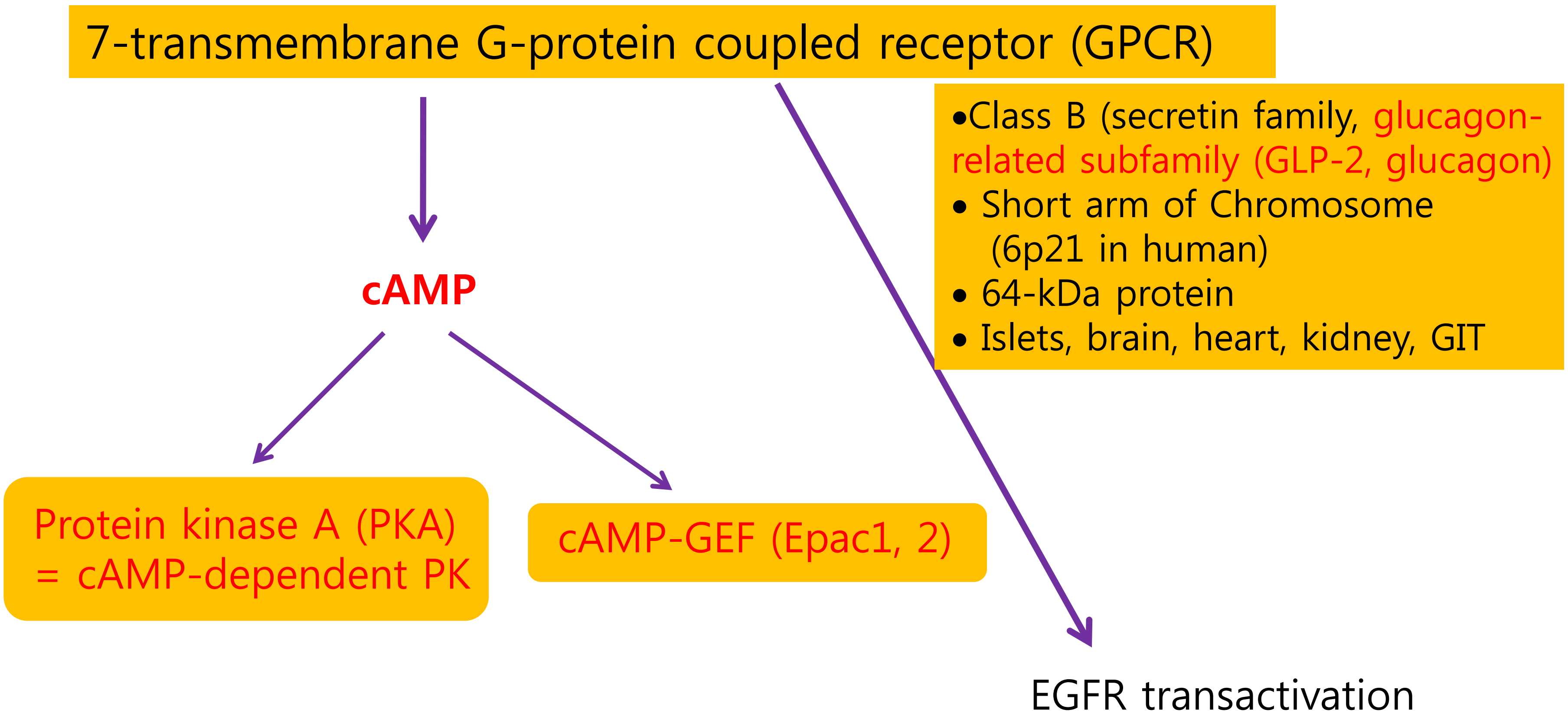
Enteroendocrine L-cell
α-cell
Brain
Taste buds



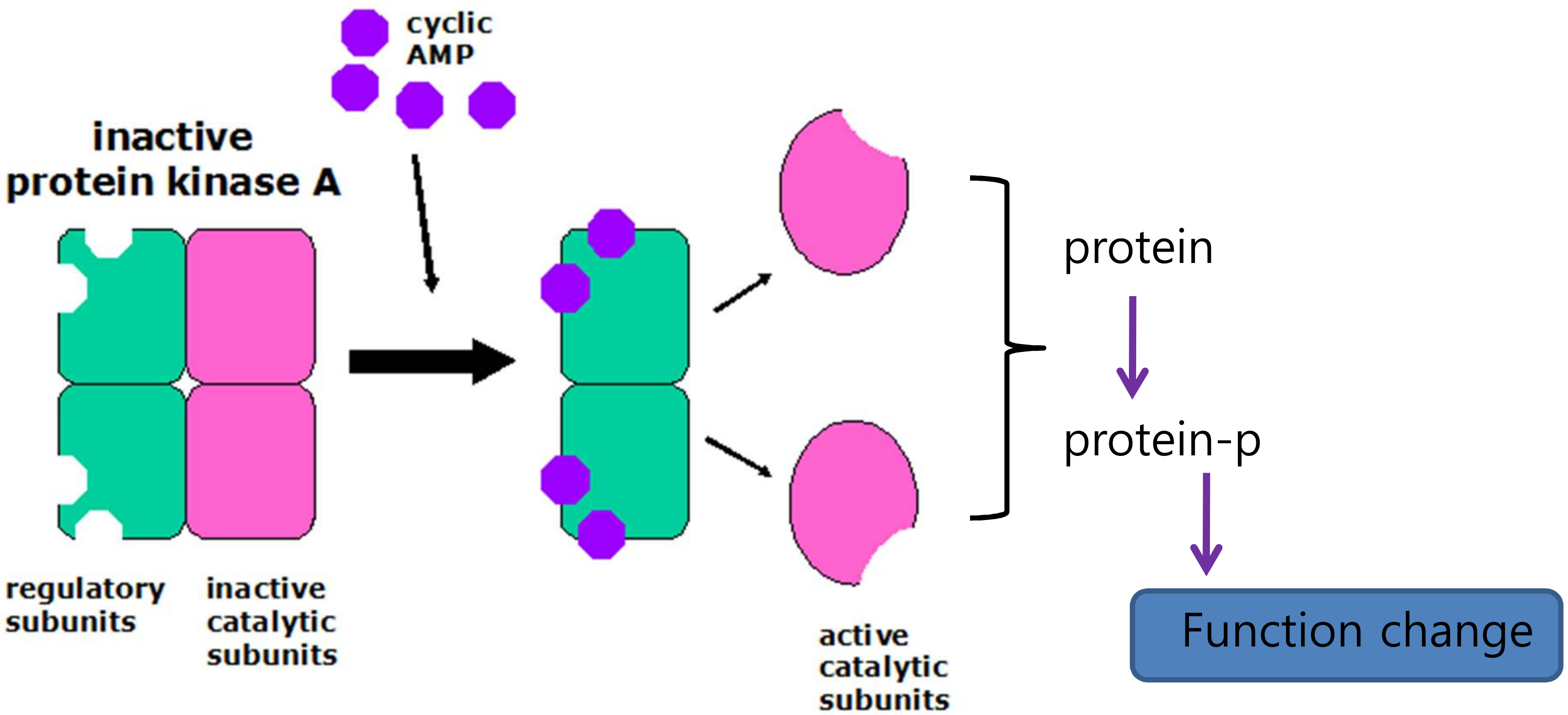
Gila monster lizard

Exendin-4
= GLP-1R agonsit

GLP-1 receptor



Protein kinase A (PKA)

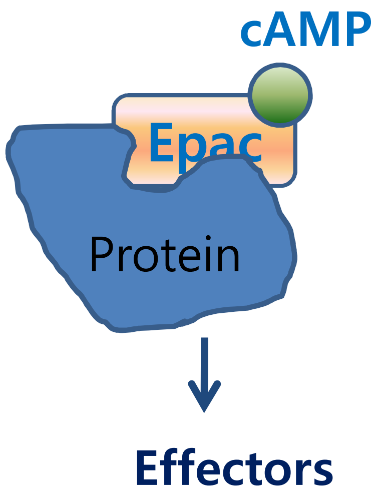


cAMP-GEF (Epac)

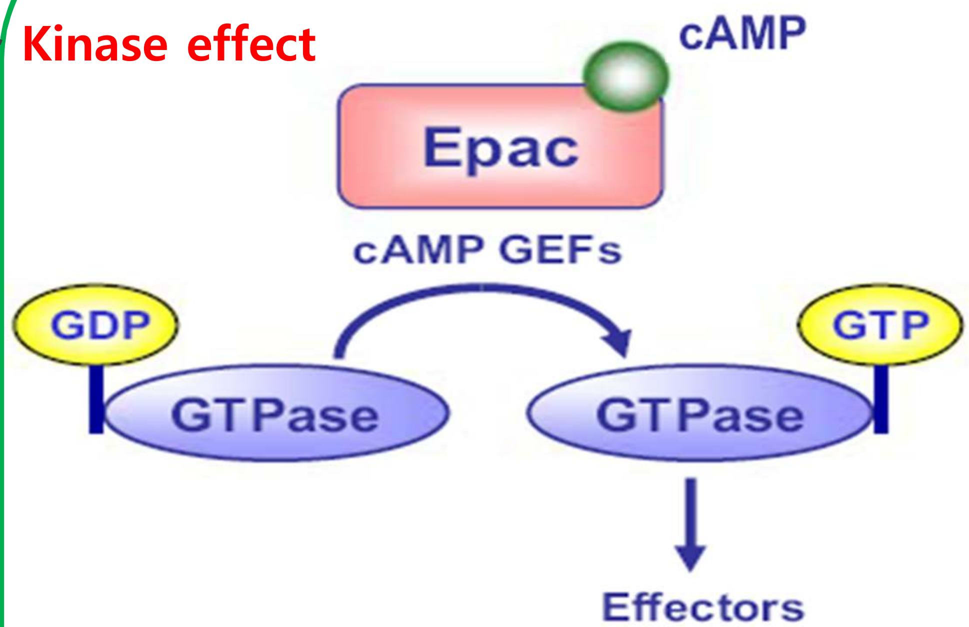
- cAMP-regulated Guanine nucleotide exchange factors
- Exchange protein directly activated by cAMP
- Two variants of Epac (*Epac1 and Epac2*)

Biological actions in beta cells

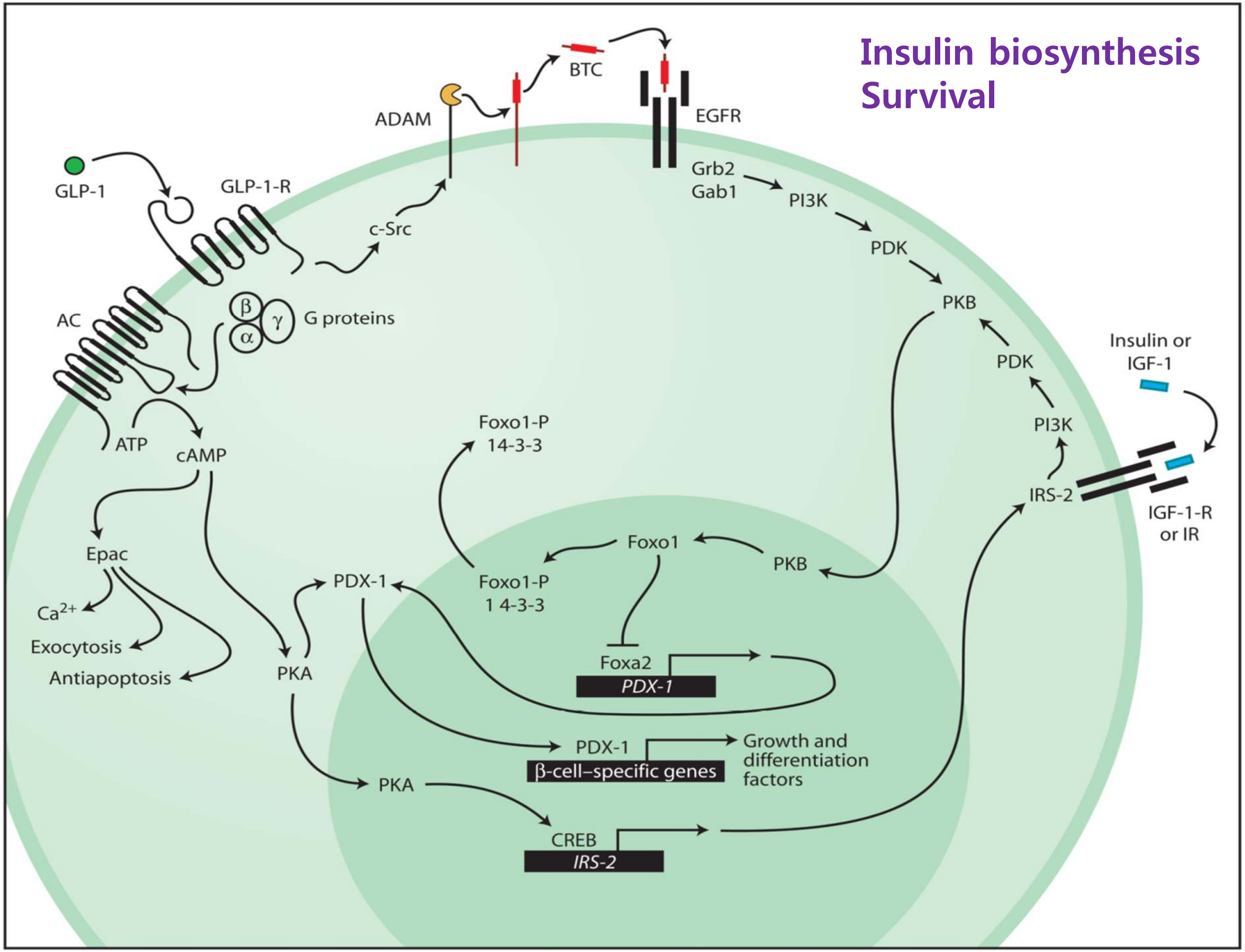
Protein-Epac complex (non-kinase effect)



Kinase effect

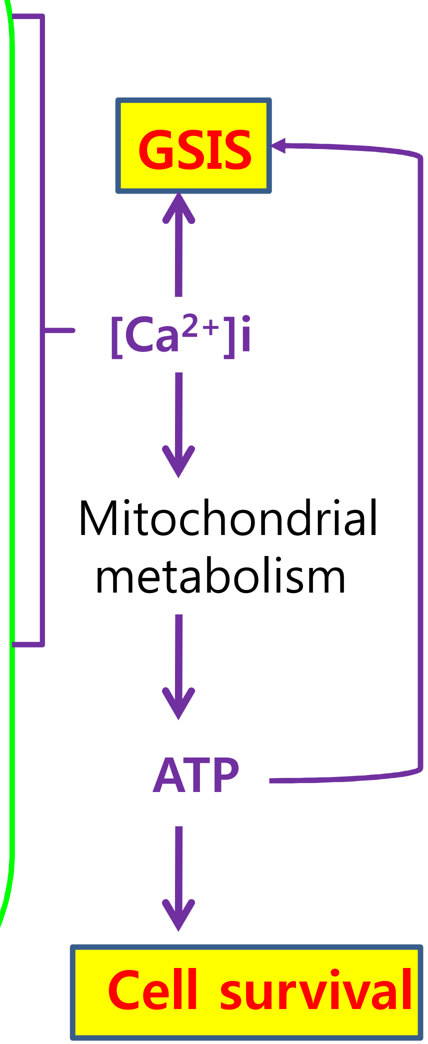


EGFR transactivation

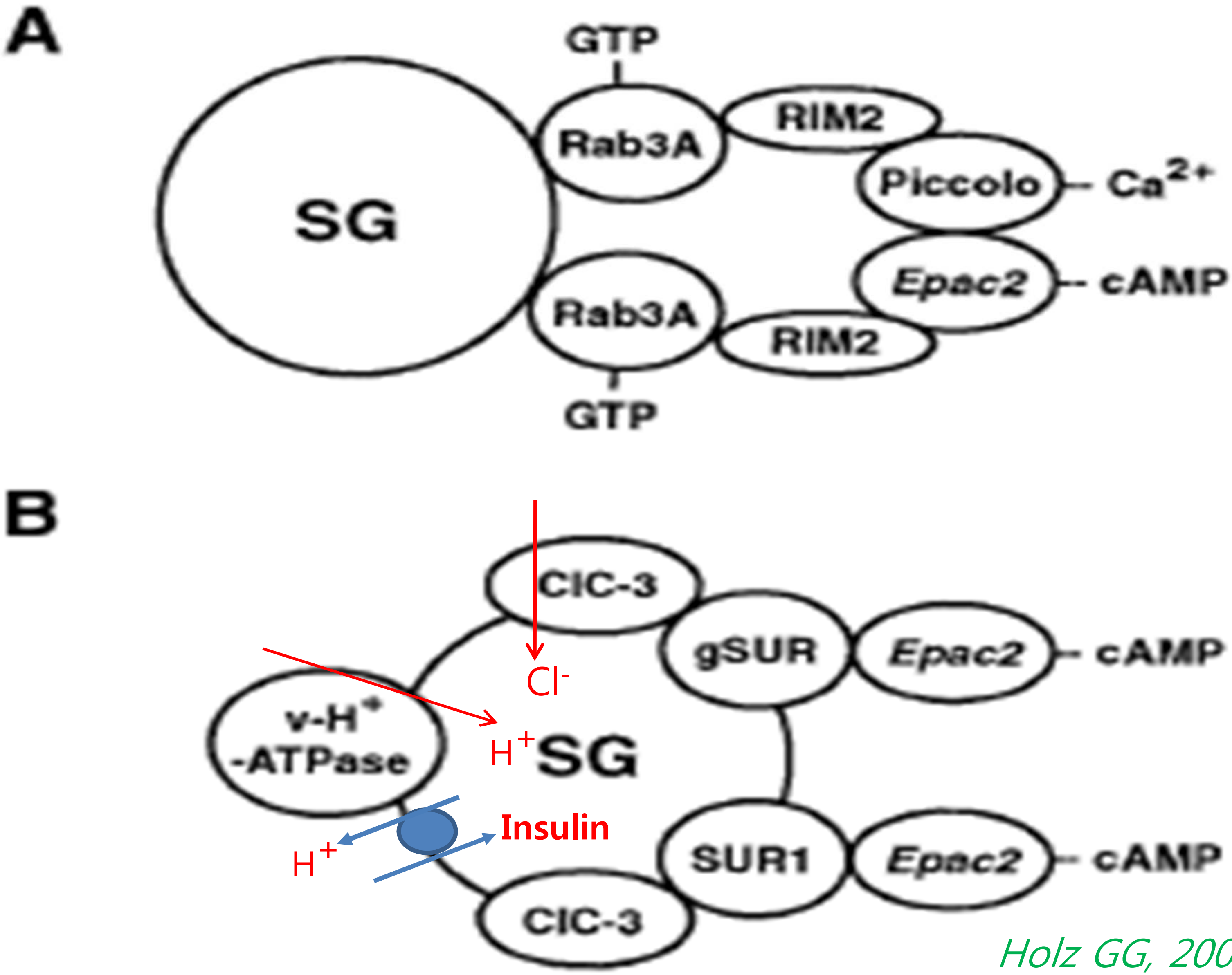


GLP-1 potentiates triggering mechanism of GSIS

	PKA	Epac
• K_{ATP}	close (SUR1)	close (SUR1)
• Kv	close	
• Cav	open	
• CICR		open(epac2)
• IP3-ICR	open	
• Secretory proteins	SNAP-25	Rim2 gSUR piccolo
• glucokinase	?	?



Amplication mechanisms of GLP-1 on GSIS



Holz GG, 2004, Diabetes

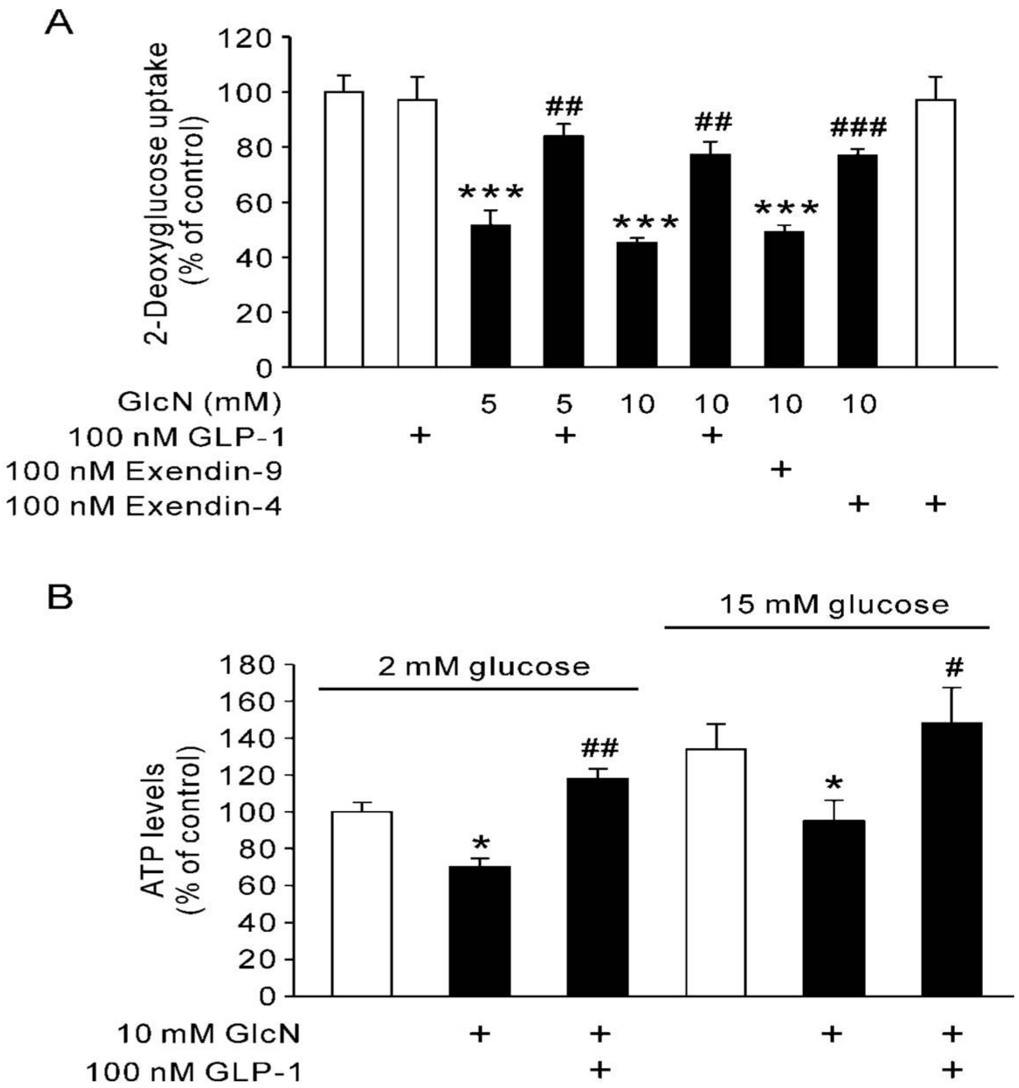
GLP-1 also potentiates glucokinase activity

β-cells
Motor neuron → ATP generation

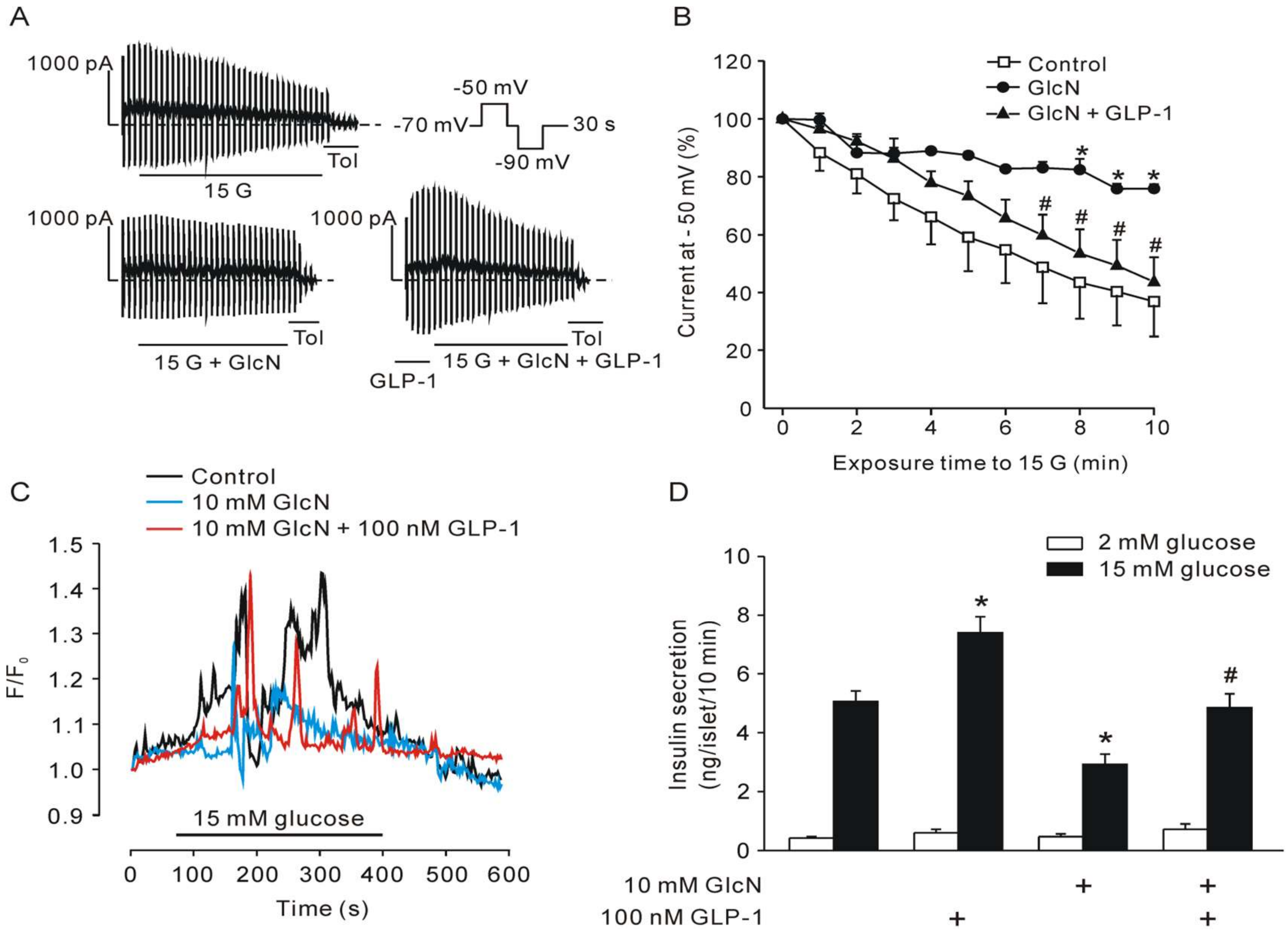
Not
Hepatocytes → Glycogen synthesis

GLP-1 potentiates glucokinase activity in β-cell & neurons

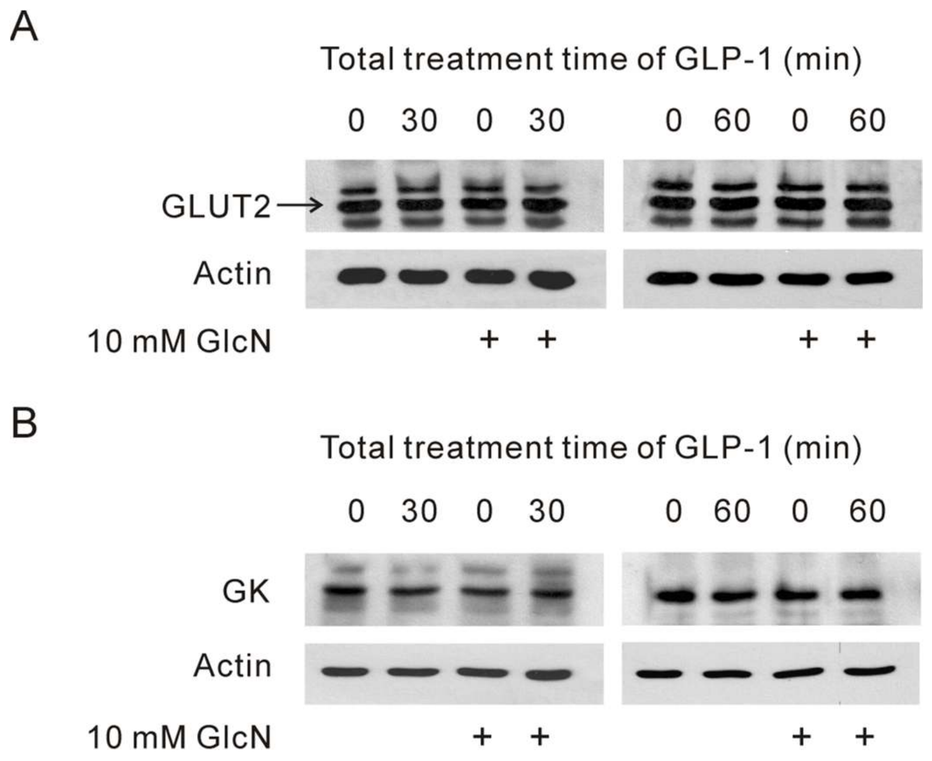
Effect of GLP-1, exendin-4, and exendin-9 on 2-deoxy-[3H]-glucose uptake and cellular ATP levels



Effect of GLP-1 on glucose-stimulated inhibition of K_{ATP} current, increase of $[Ca^{2+}]_c$ and insulin secretion

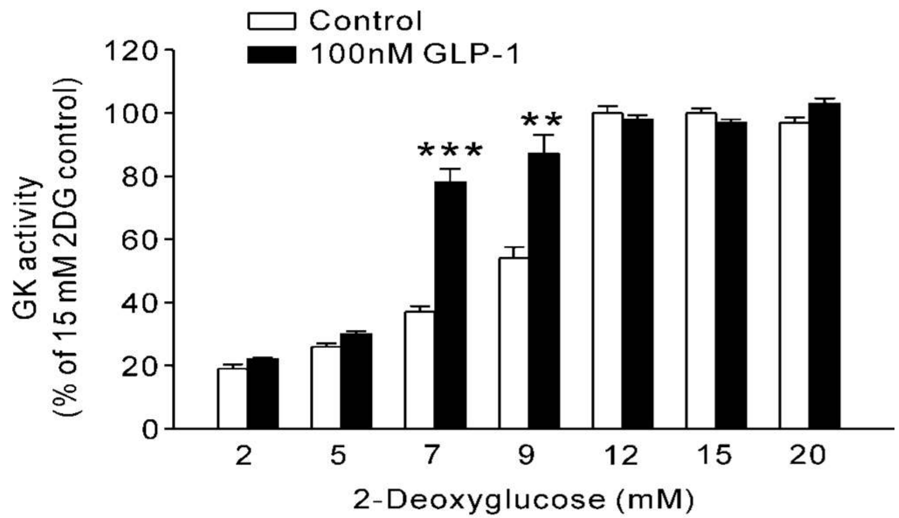


Effect of GLP-1 on GLUT2 and GK expression

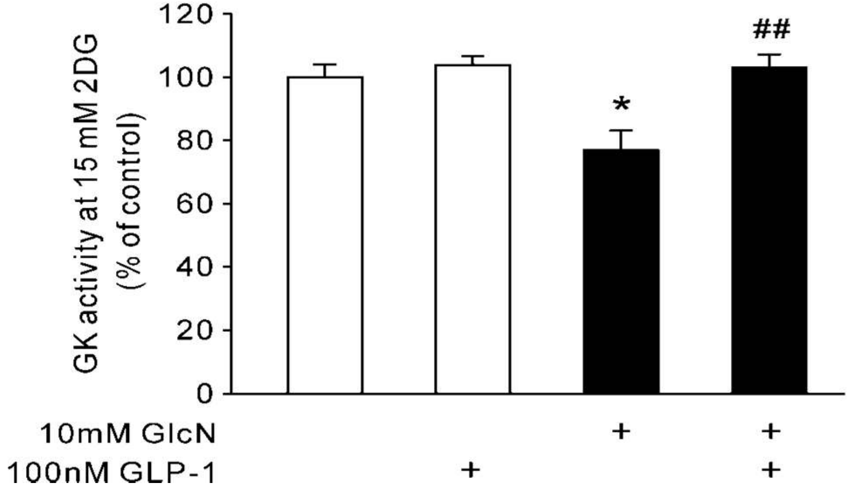


Effect of GLP-1 on GK activity

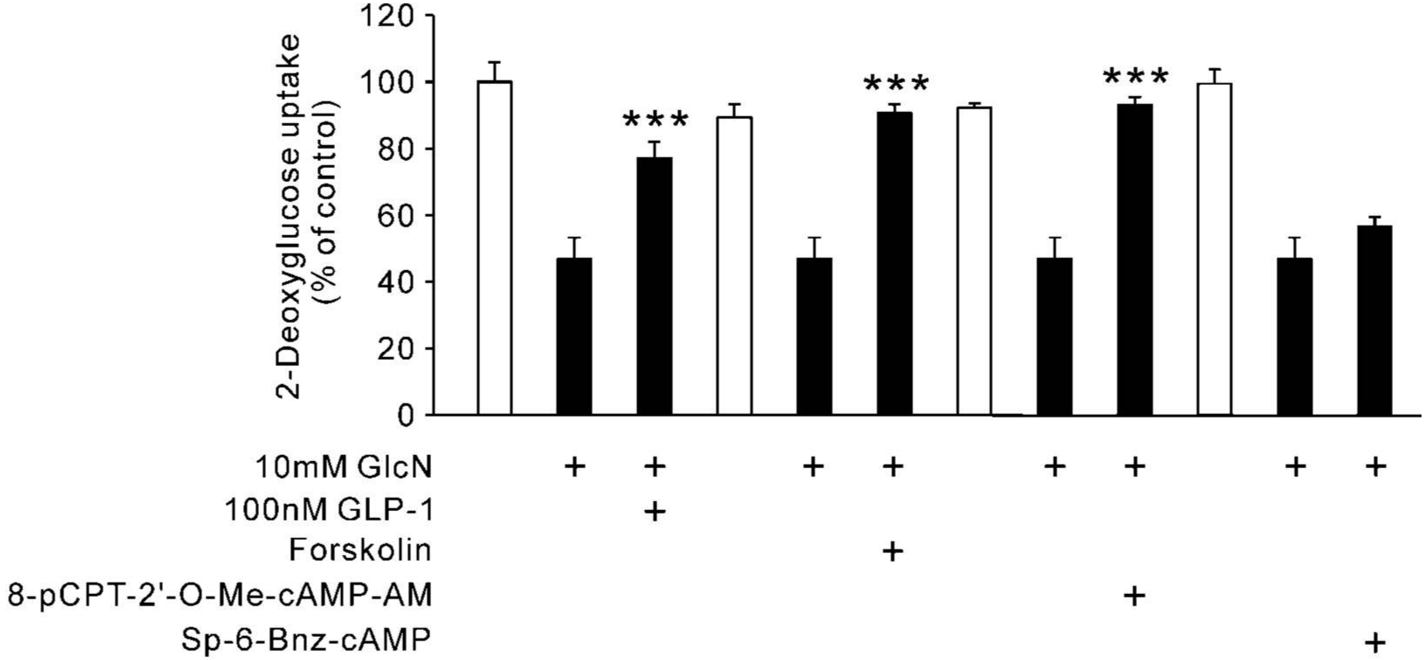
A



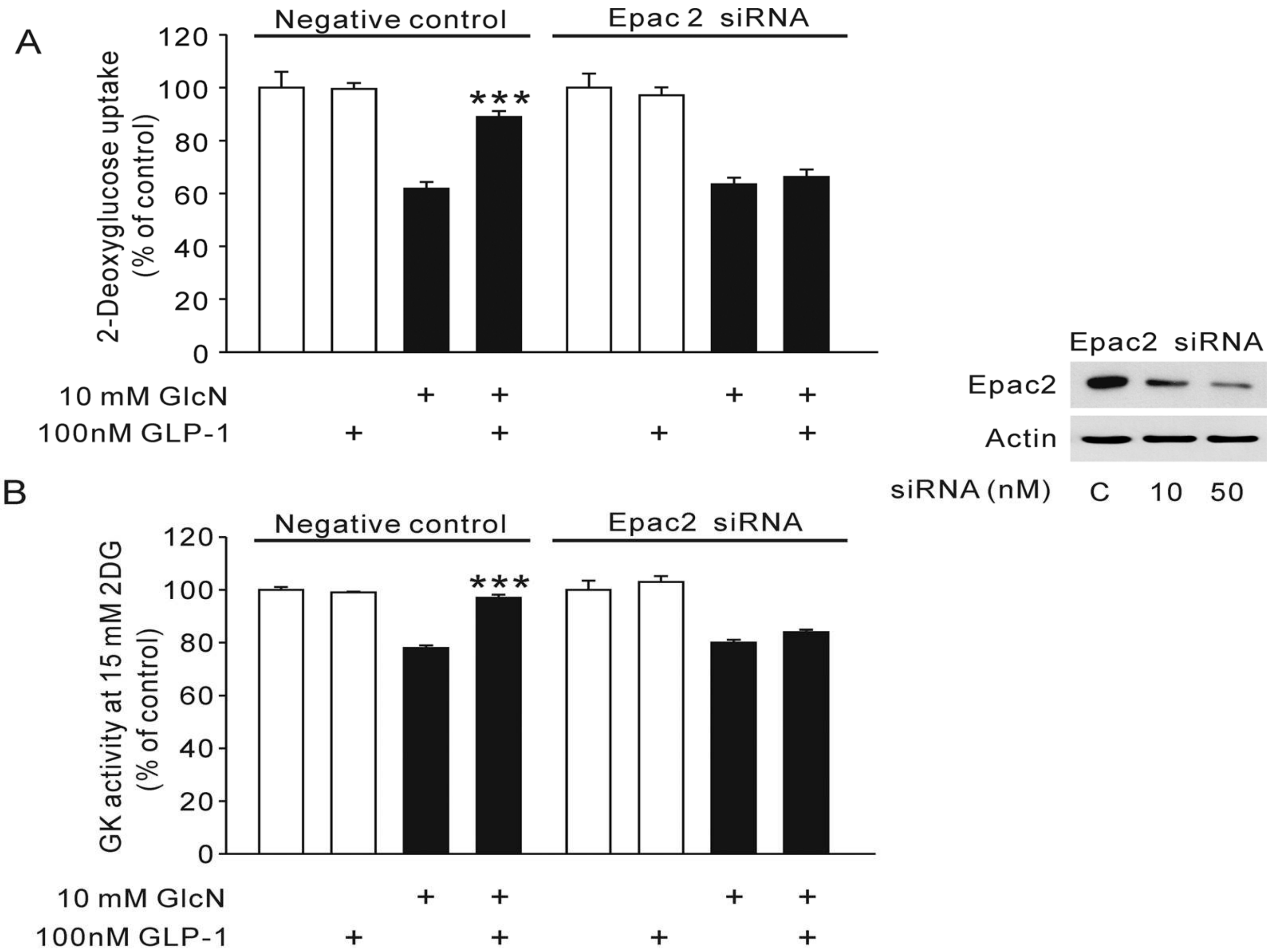
B



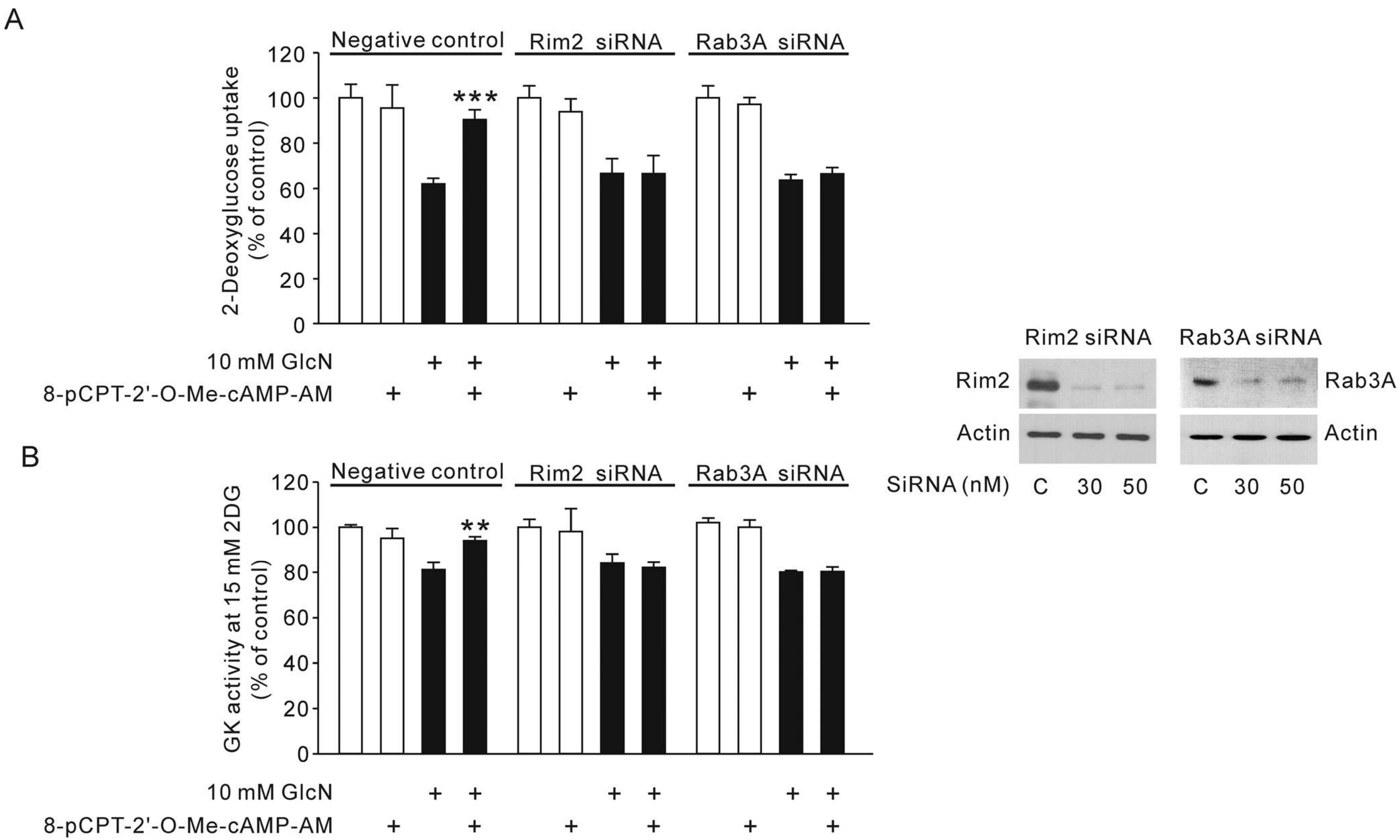
Involvement of cAMP and Epac in the restorative effects of GLP-1 on 2-deoxyglucose uptake



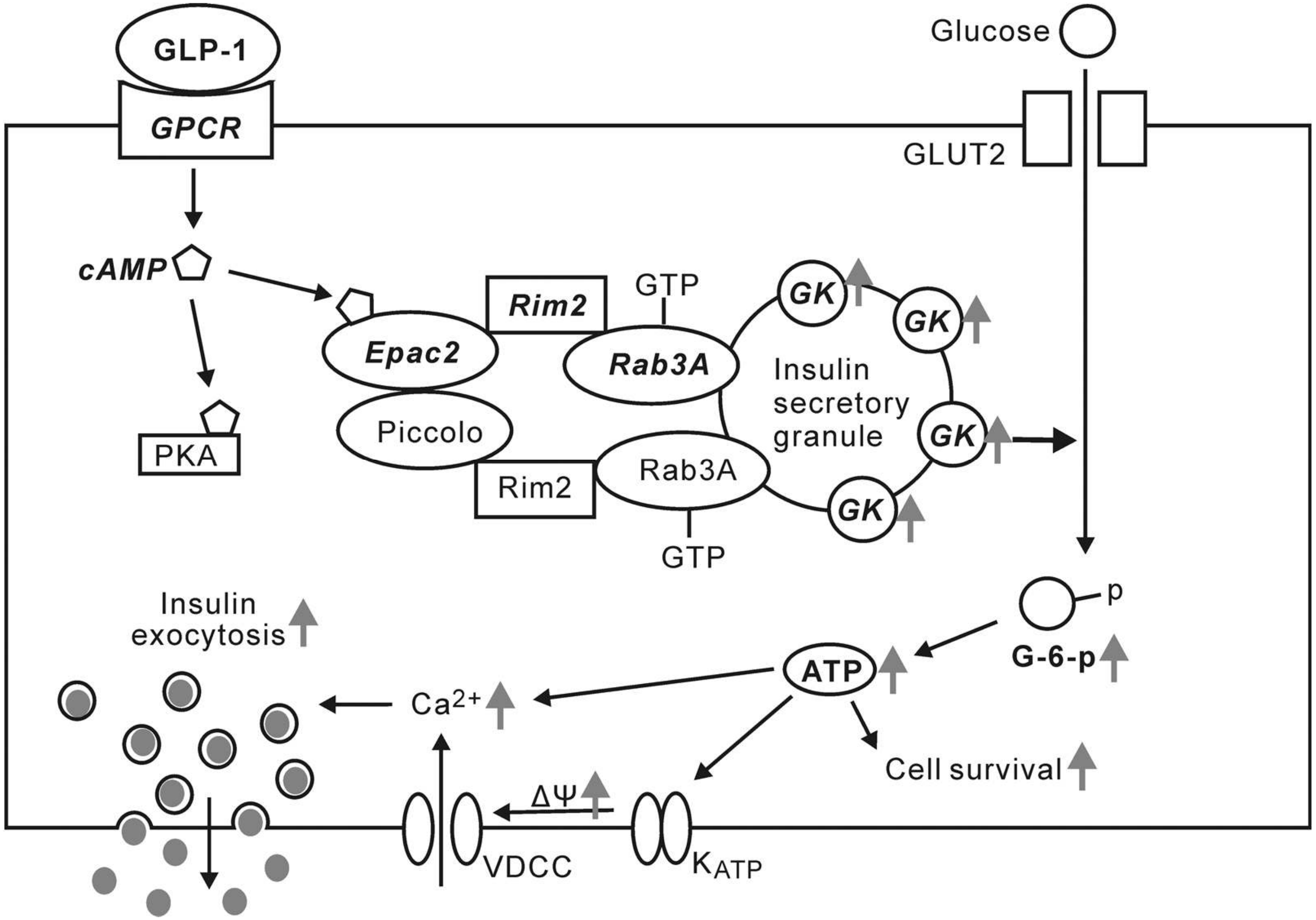
Restorative effect of GLP-1 in Epac2-knockdown INS-1 cells



Restorative effect of GLP-1 in Rim2- or Rab3A-knockdown INS-1 cells



Proposed mechanism to explain the effects of GLP-1 on GK activity



Motor neuron cell line

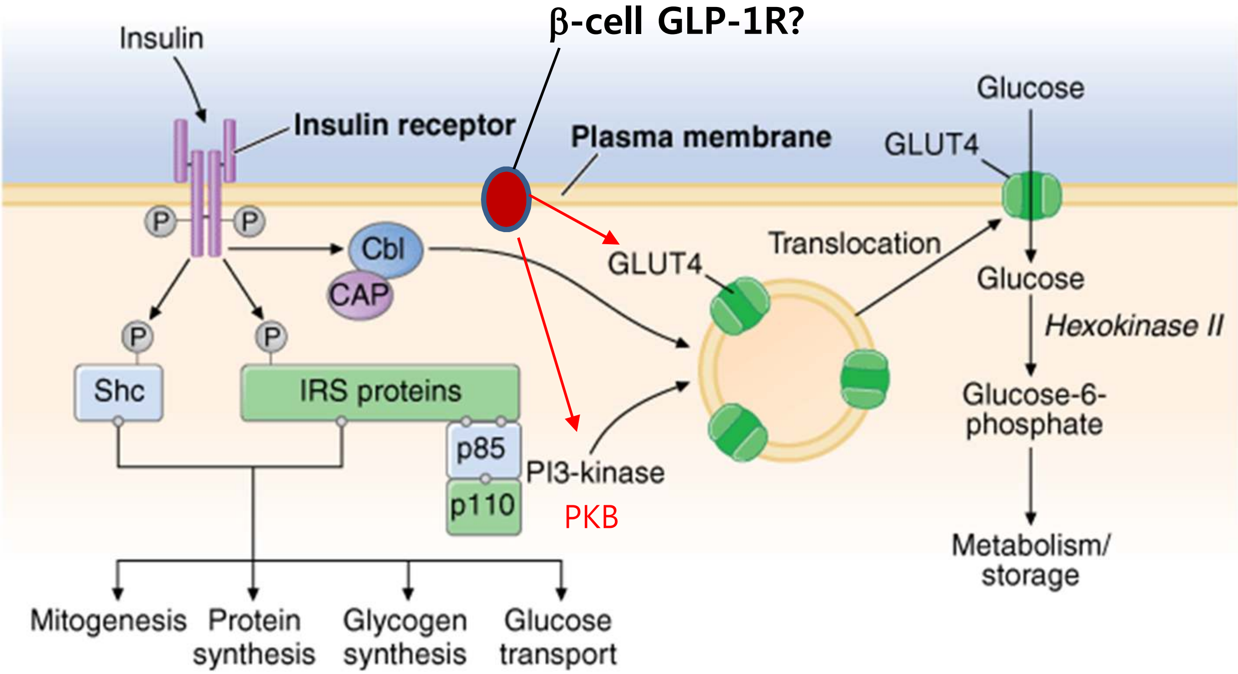
Effect of GLP-1 on 2-deoxy-[^{3}H]-glucose uptake, glucokinase (GK) activity and intracellular ATP levels against glucosamine (GlcN)

	Control	GLP-1 (100 nM)	GlcN (10 mM)	GlcN (10 mM)	
				GLP-1 (100 nM)	MP (1 mM)
Glucose uptake (%)	100.0 ± 2.3	103.6 ± 3.5	63.4 ± 2.6***	85.2 ± 2.9###	–
GK activity (%)	100.0 ± 4.0	104.0 ± 2.8	76.3 ± 6.4**	103.7 ± 4.0##	–
Cellular ATP level (%)	100.0 ± 2.5	103.3 ± 4.2	78.6 ± 1.6***	92.0 ± 2.7#	98.9 ± 2.8###

	Control	GlcN (10mM)	GlcN (10 mM)		
			GLP-1 (100 nM)	8-pCPT-2-Me-cAMP (50 μM)	SP-6-Bnz-cAMPS (50 μM)
Control	100.0 ± 2.3	63.4 ± 2.6	85.2 ± 2.9***	**82.2 ± 3.7*****	61.7 ± 5.5
Wortmannin (0.5 μM)	86.4 ± 5.5	48.8 ± 4.8	77.3 ± 4.4*	–	–
LY294002 (10 μM)	88.8 ± 6.5	47.5 ± 3.5	77.8 ± 4.4**	–	–
H-89 (10 μM)	93.4 ± 4.8	47.4 ± 3.0	78.6 ± 2.5**	–	–
MDL (10 μM)	91.3 ± 3.4	48.7 ± 4.7	**55.7 ± 4.2**	–	–
PP1 (10 μM)	95.3 ± 5.1	48.5 ± 4.4	78.8 ± 4.1**	–	–
AG1478 (250 nM)	95.1 ± 5.0	47.0 ± 4.7	75.8 ± 4.4*	–	–

Neurosci Lett, 2010

muscle and adipocytes

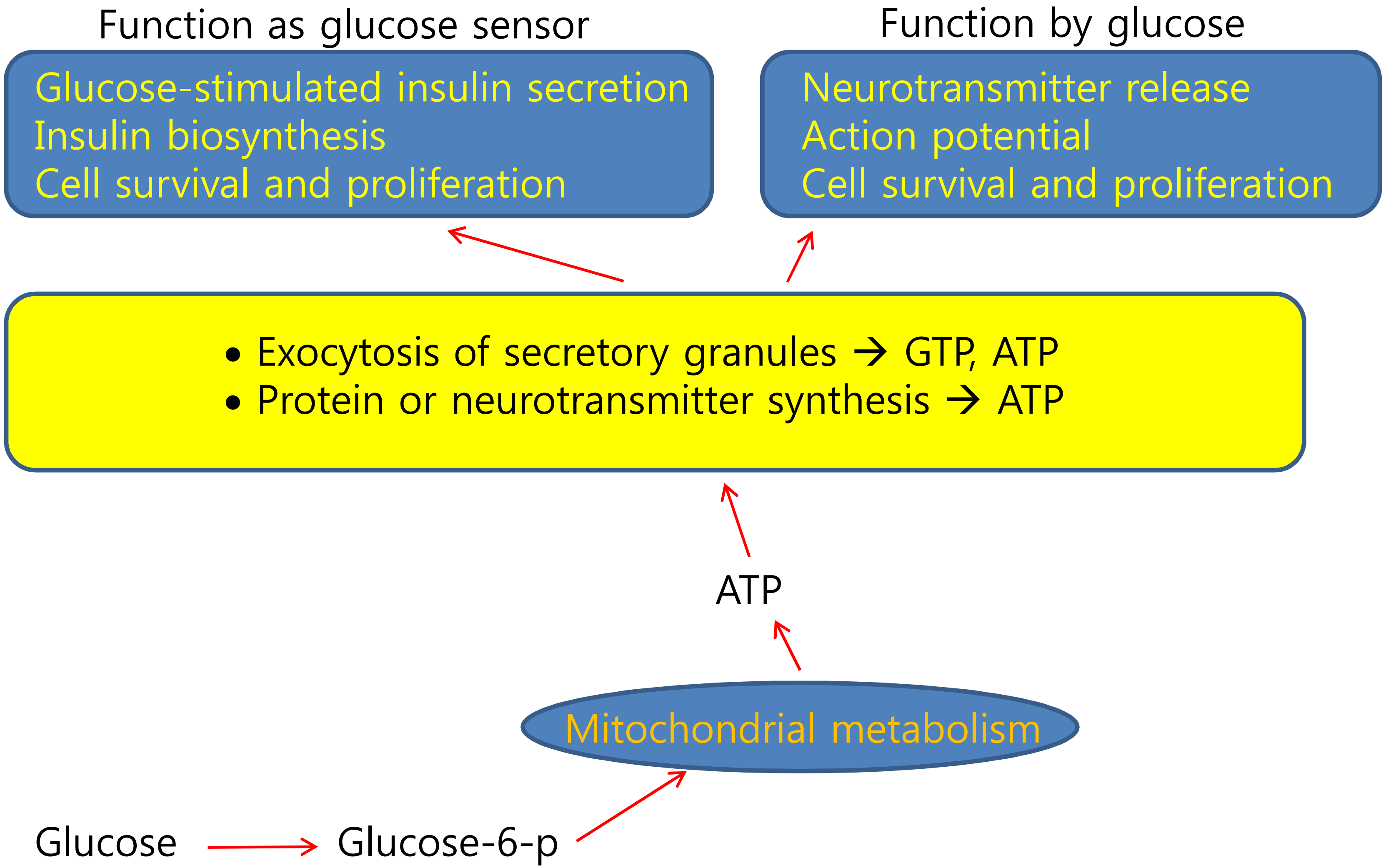


hepatocytes

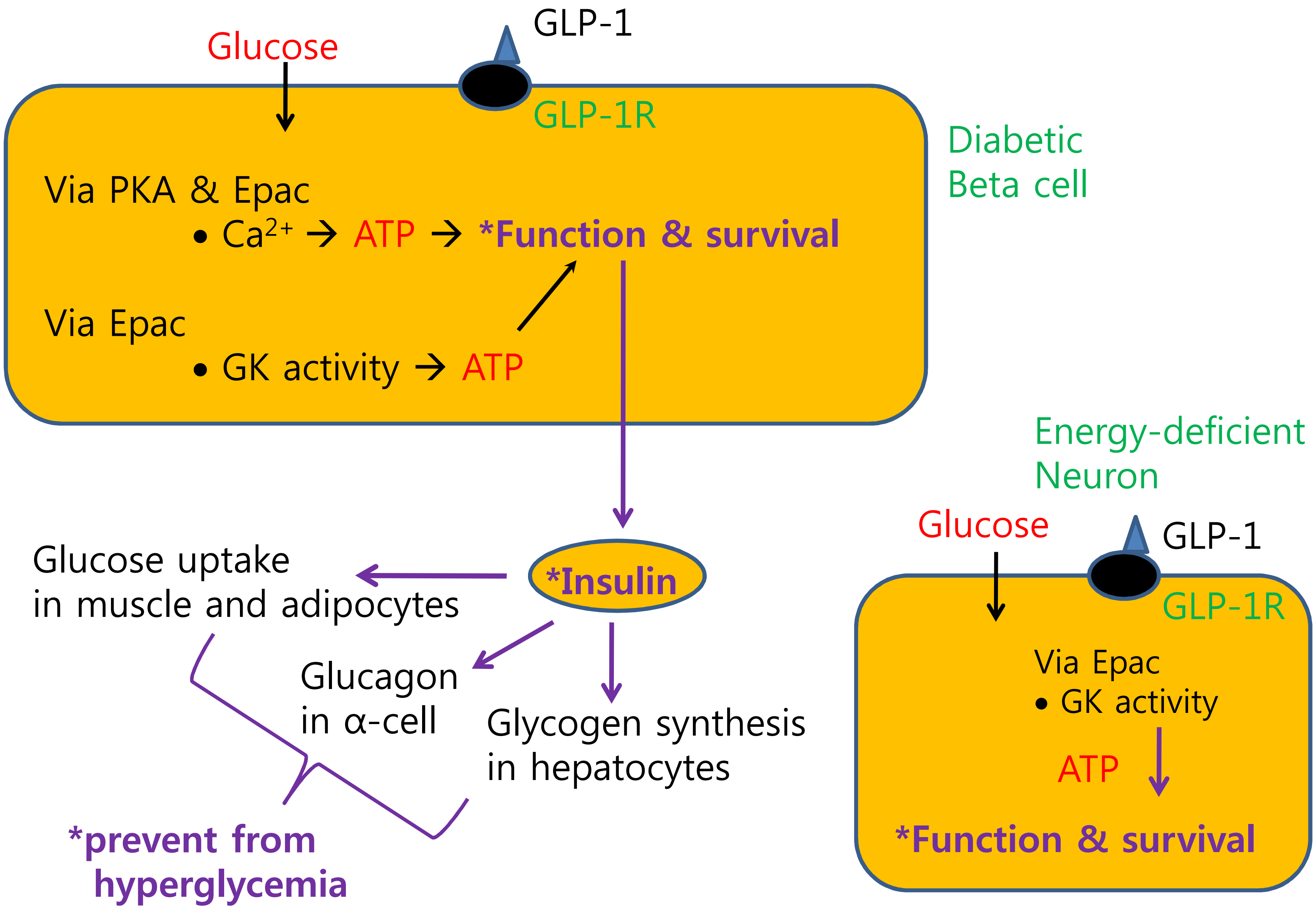
β-cell GLP-1R?
Unknown signaling mechanism
Long-term Tx → GLUT2 expression, glycogen synthesis enzyme

GLP-1 or its analogues effects → long-term effect only via non-GLP-1R

Greater glucose-metabolism dependency of β-cells & neurons on action



Summary



GLP-1
Glucose
GLP-1R
Diabetic Beta cell
Via PKA & Epac
• Ca2+ → ATP → *Function & survival
Via Epac
• GK activity → ATP
*Insulin
Glucose uptake in muscle and adipocytes
Glucagon in α-cell
Glycogen synthesis in hepatocytes
*prevent from hyperglycemia
Energy-deficient Neuron
Glucose
GLP-1
GLP-1R
Via Epac
• GK activity
ATP
*Function & survival

Conclusions
with our observations and previous reports

● GLP-1 may **insulin-independently potentiate glucose sensitivity** in diabetic **β-cells and neurons**.

● Effect of GLP-1 on the **other insulin-sensitive tissues** may be due to **ameliorated I/G ratio** by GLP-1.

감사합니다