
خدای من
همین نزدیکی است...

Aquaporin's in insulin resistance and diabetes: More than channels!

Nepton Soltani

DIABETES

DIABETES MELLITUS

Type 2
inability of insulin-sensitive tissues(receptor) to respond to insulin.

↓

Insulin Resistance

Type 1
autoimmune destruction of insulin-producing beta cells in the pancreas.

↓

↓ Insulin

Insulin resistance

■ **Pancreas**
: **Reduced/altered insulin secretion**

▪ ***Endocrine hormones***
: Insulin (β-cells)
: Glucagon (α-cells)

▪ **Obesity & Type II diabetes**
: Insulin resistance /Hyperglycemia

(Hepatokines ↑)

(Myokines ↓)

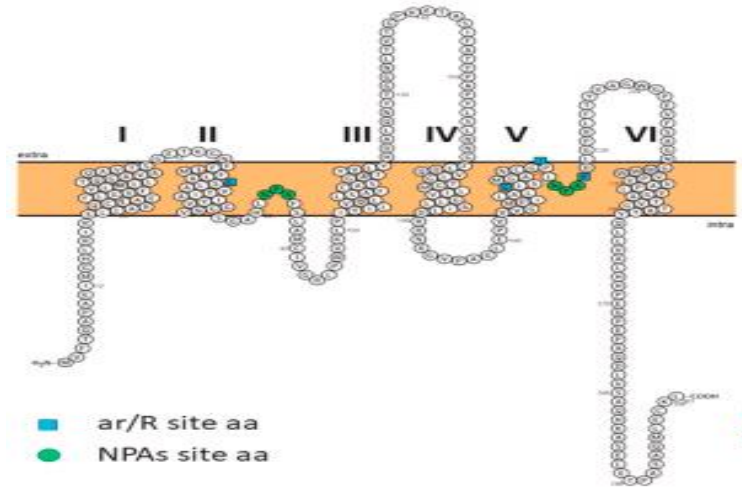
(Pro-inflammatory adipokines ↑)
(Anti-inflammatory adipokines ↓)

■ **Liver**
: Inappropriate glucose production

■ **Muscle**
: Impaired insulin-mediated glucose disposal

■ **Adipose tissue**
: Release of increased FFA
& Excessive accumulation of adipose tissue

Aquaporin's Structure



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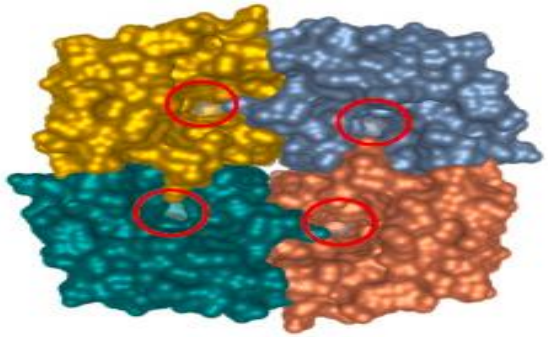

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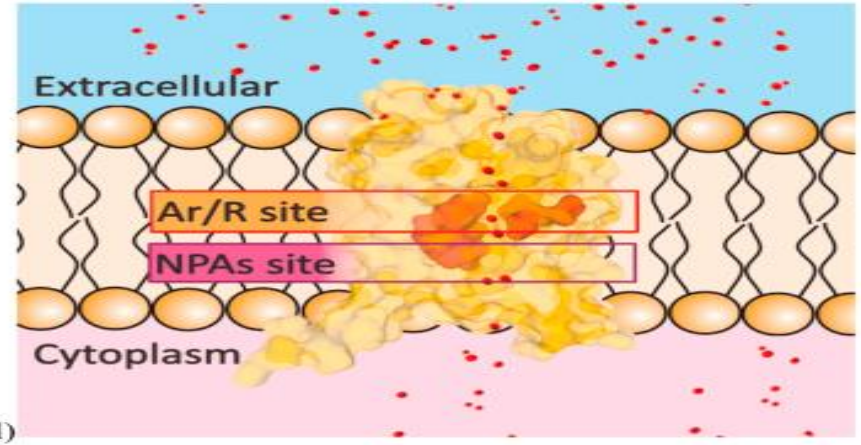
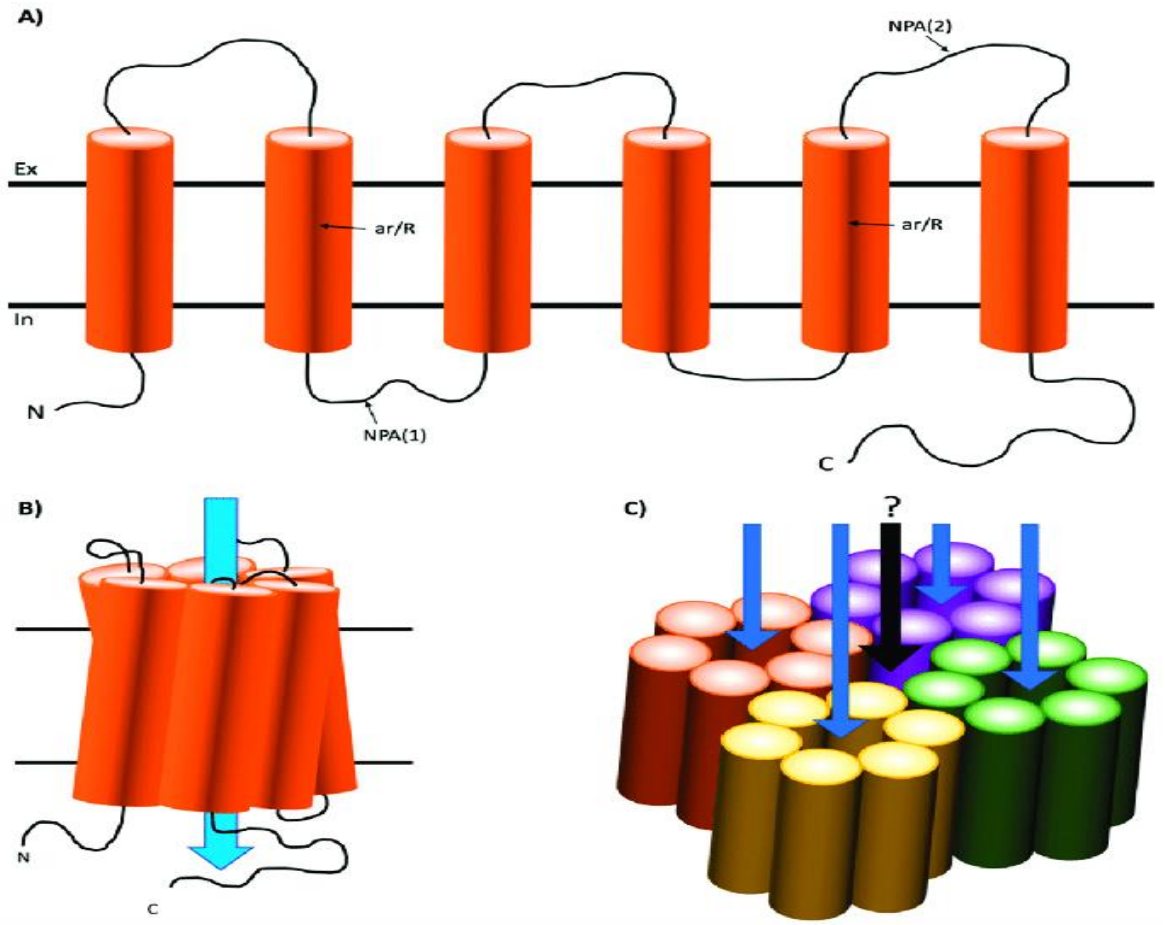
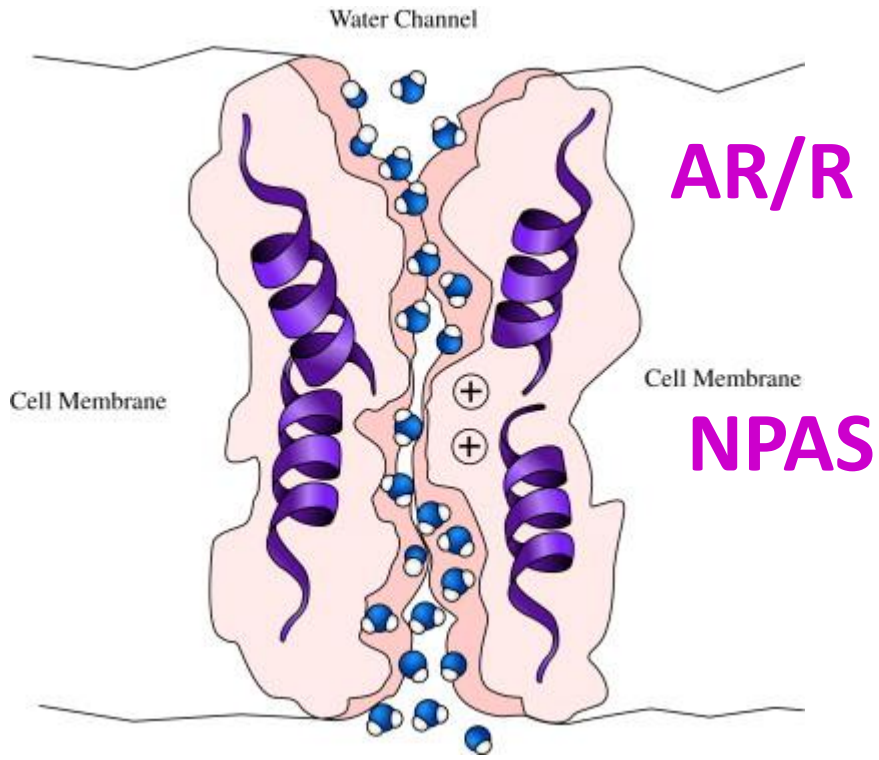


(d)

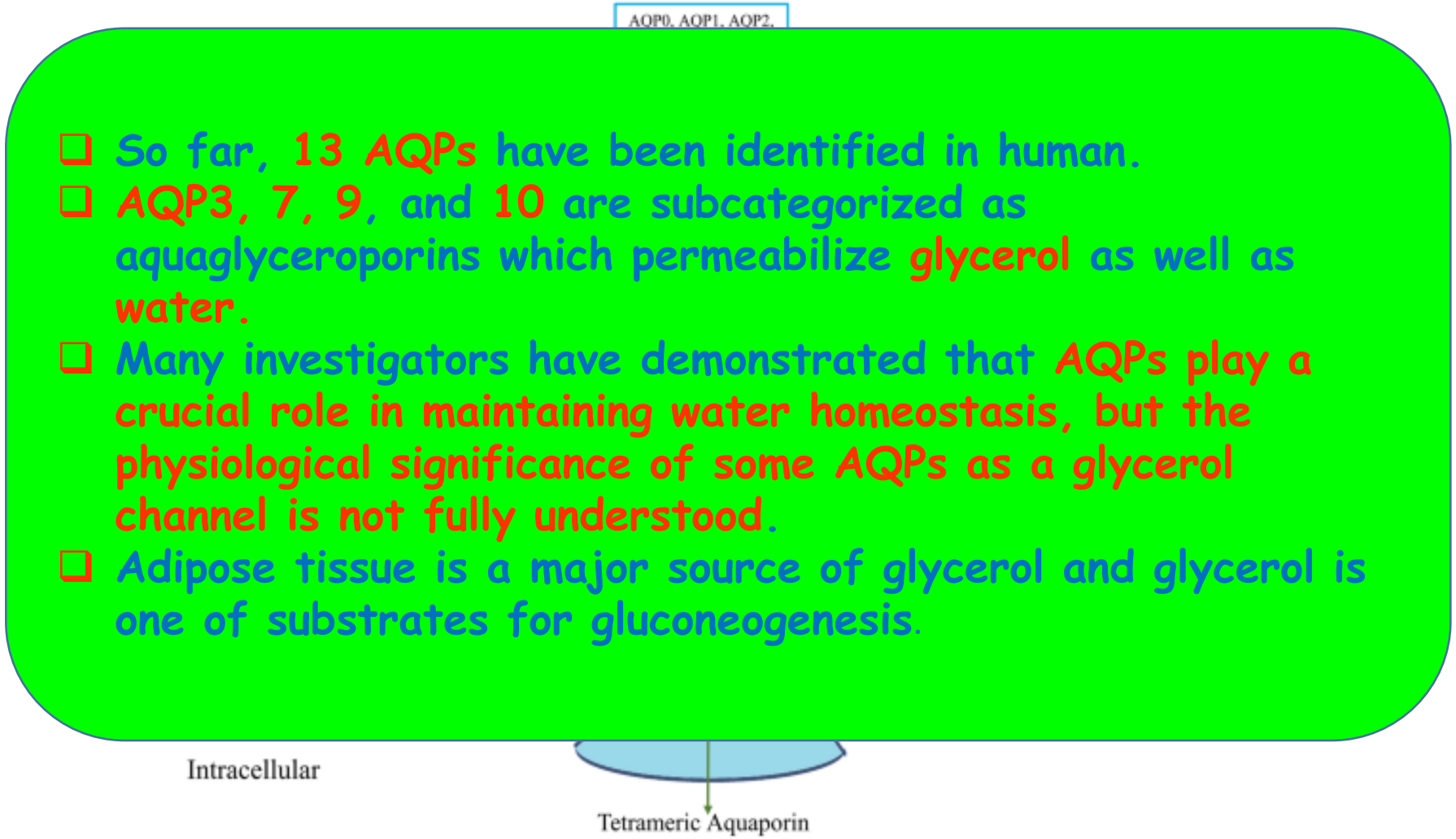
Aquaporin's Structure



Aquaporin's Structure

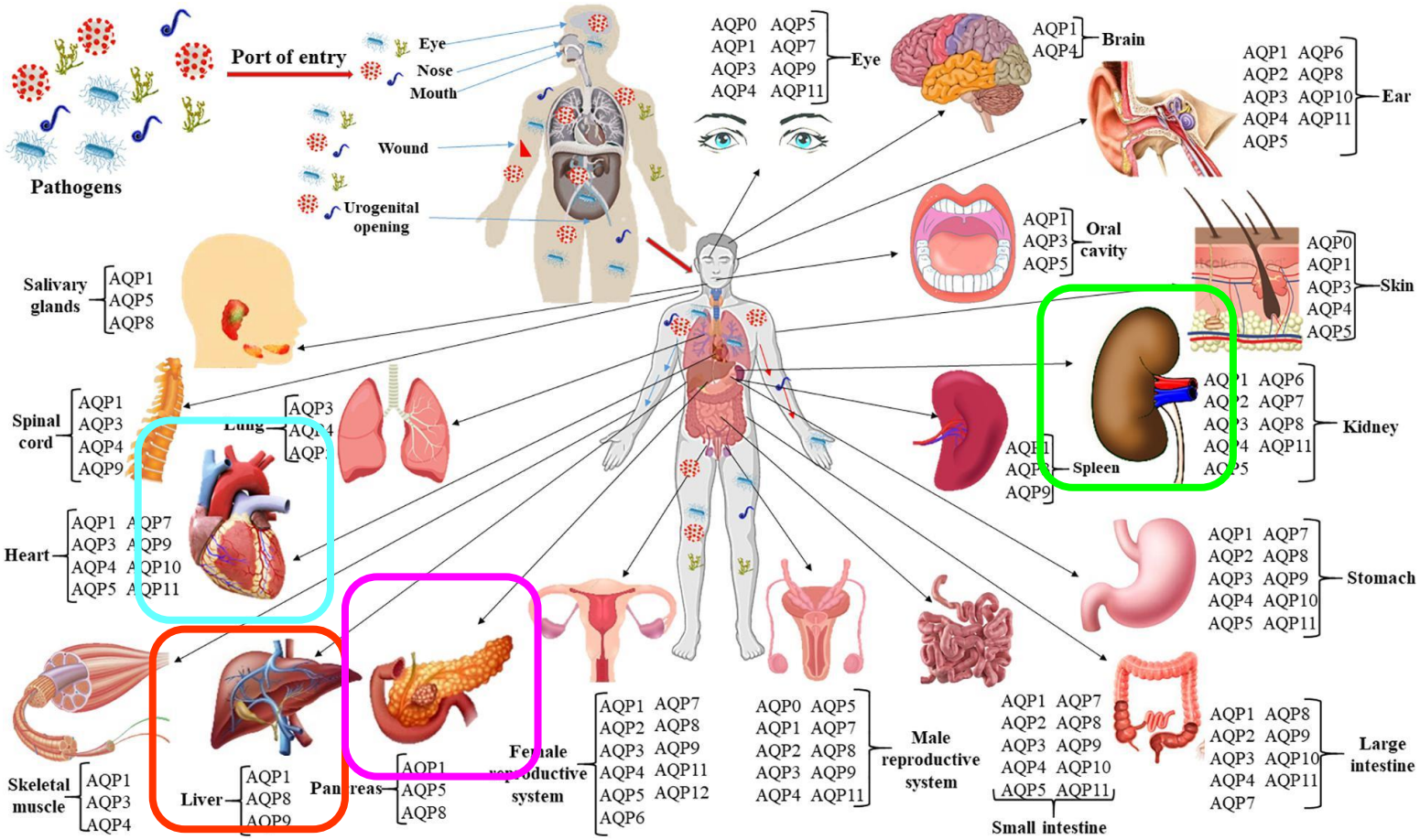


Different kinds of aquaporin's

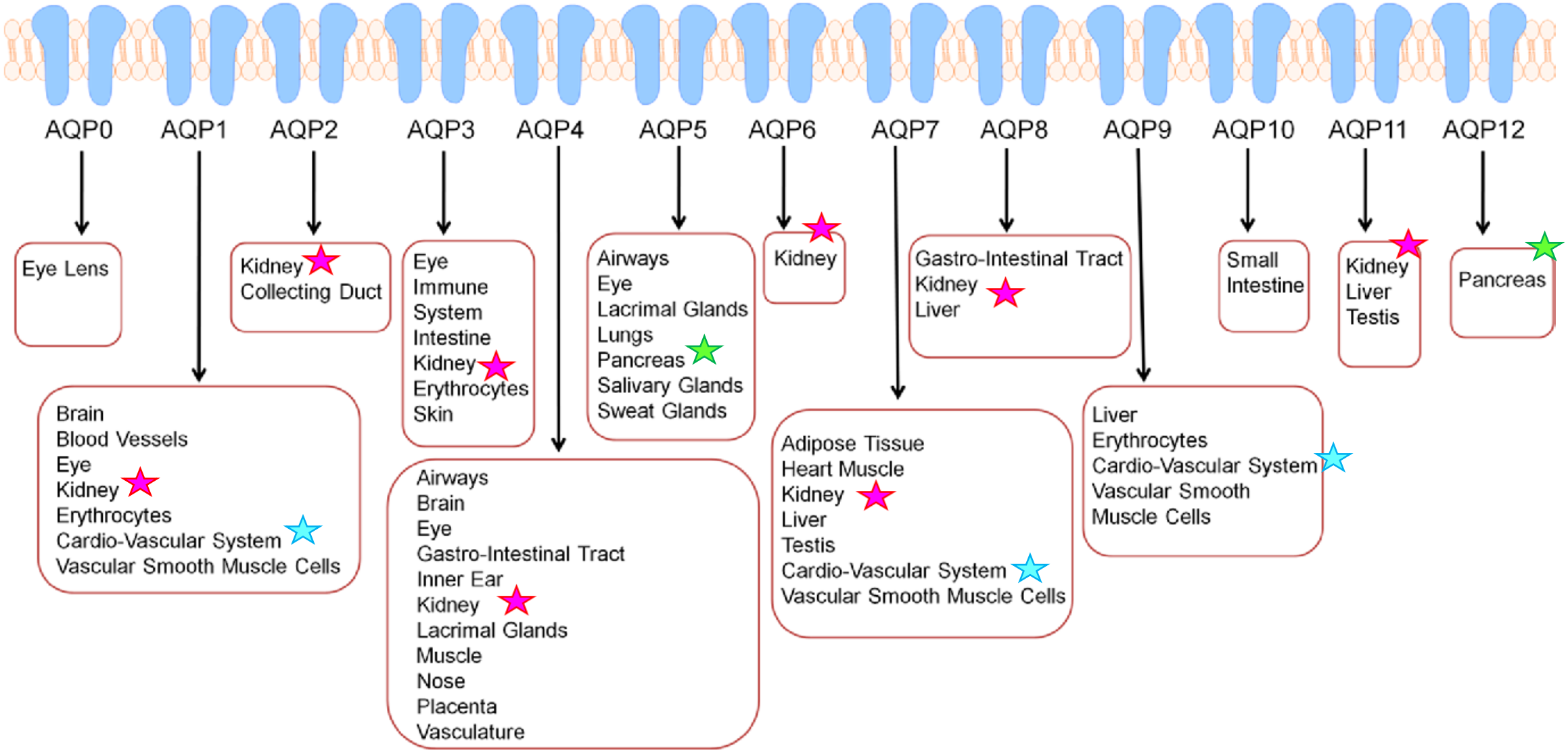


- So far, 13 AQPs have been identified in human.
- AQP3, 7, 9, and 10 are subcategorized as aquaglyceroporins which permeabilize glycerol as well as water.
- Many investigators have demonstrated that AQPs play a crucial role in maintaining water homeostasis, but the physiological significance of some AQPs as a glycerol channel is not fully understood.
- Adipose tissue is a major source of glycerol and glycerol is one of substrates for gluconeogenesis.

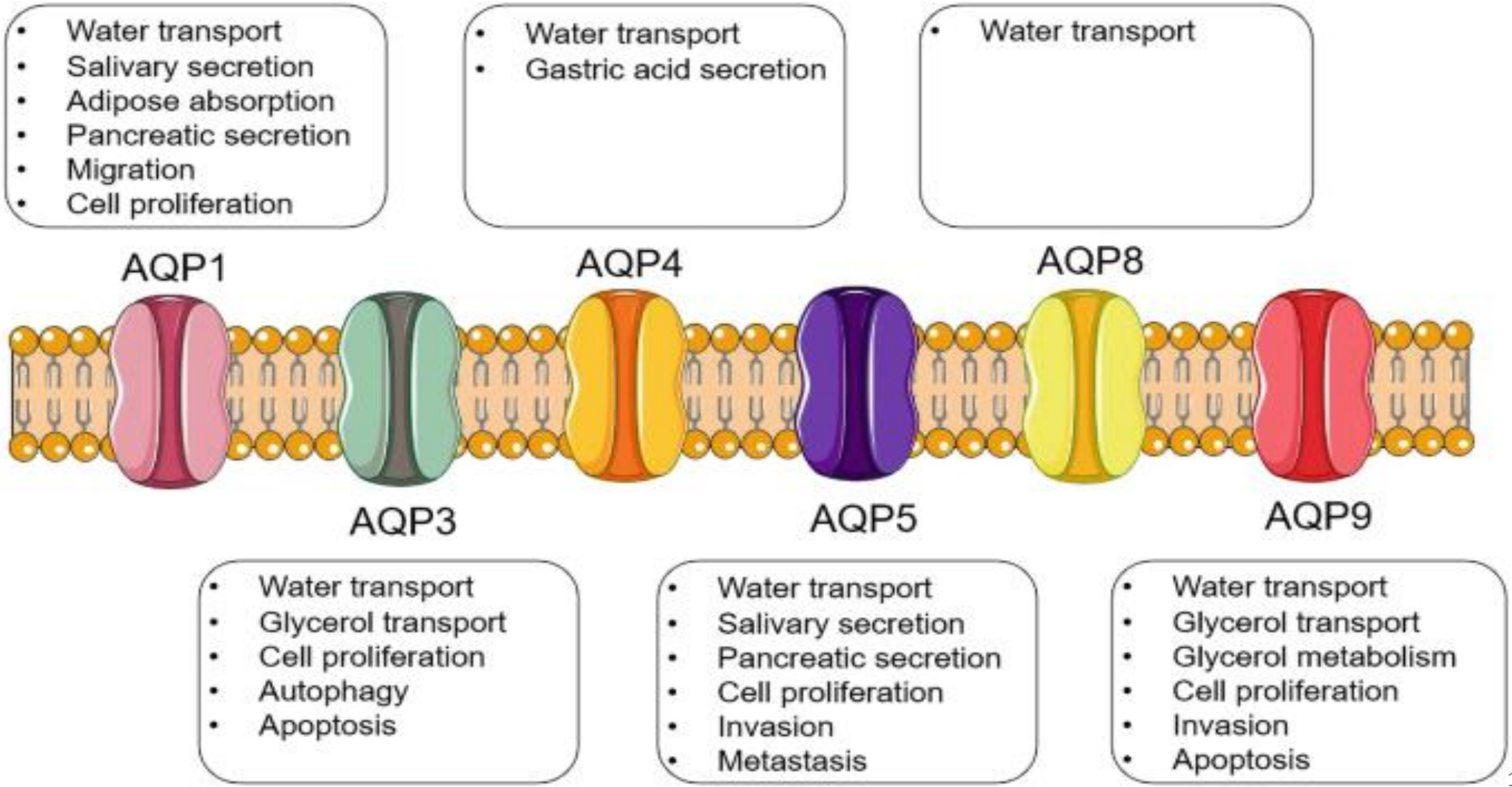
Aquaporin's channel distribution



Aquaporin's channel distribution



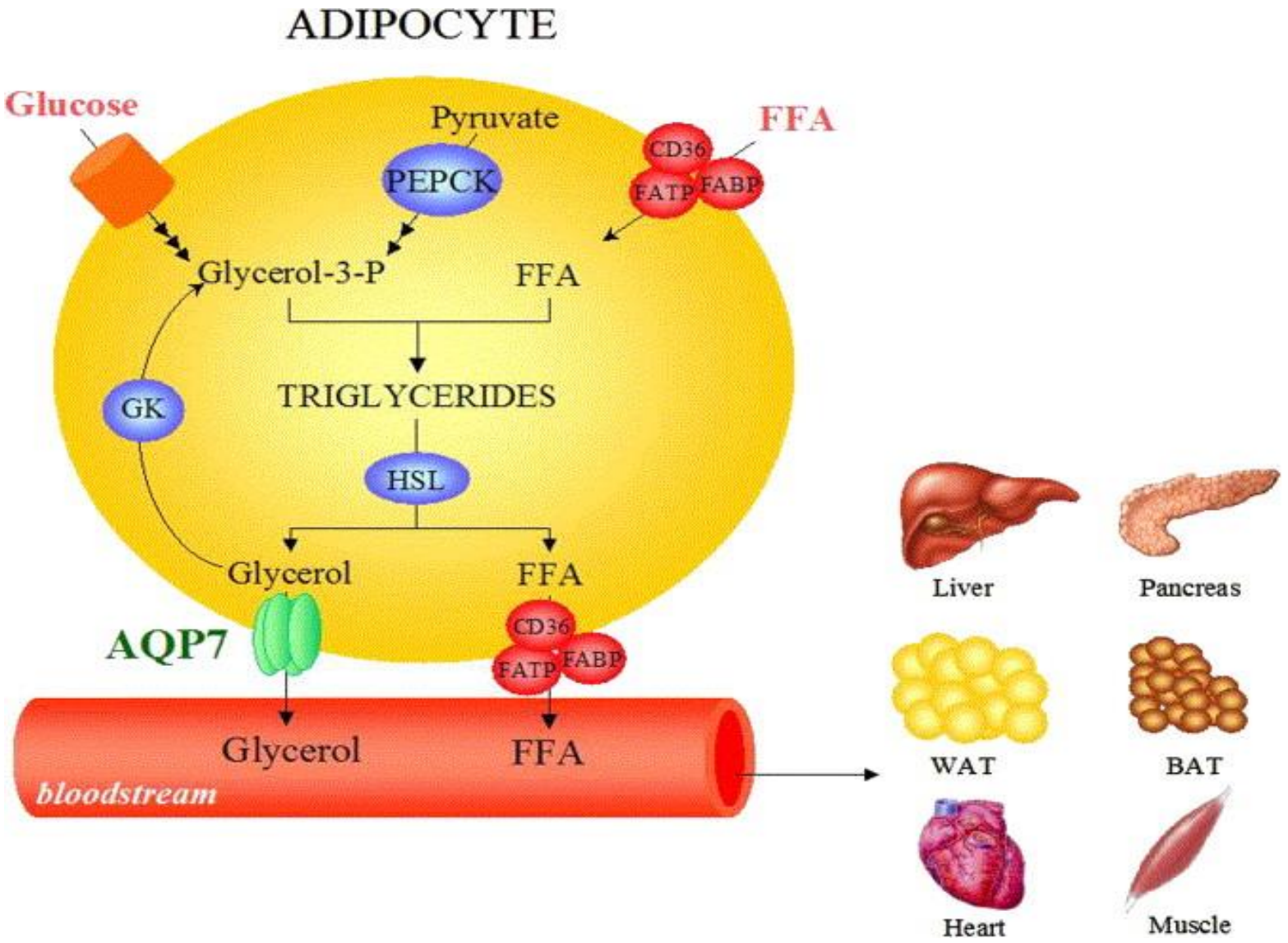
Aquaporin's channel action



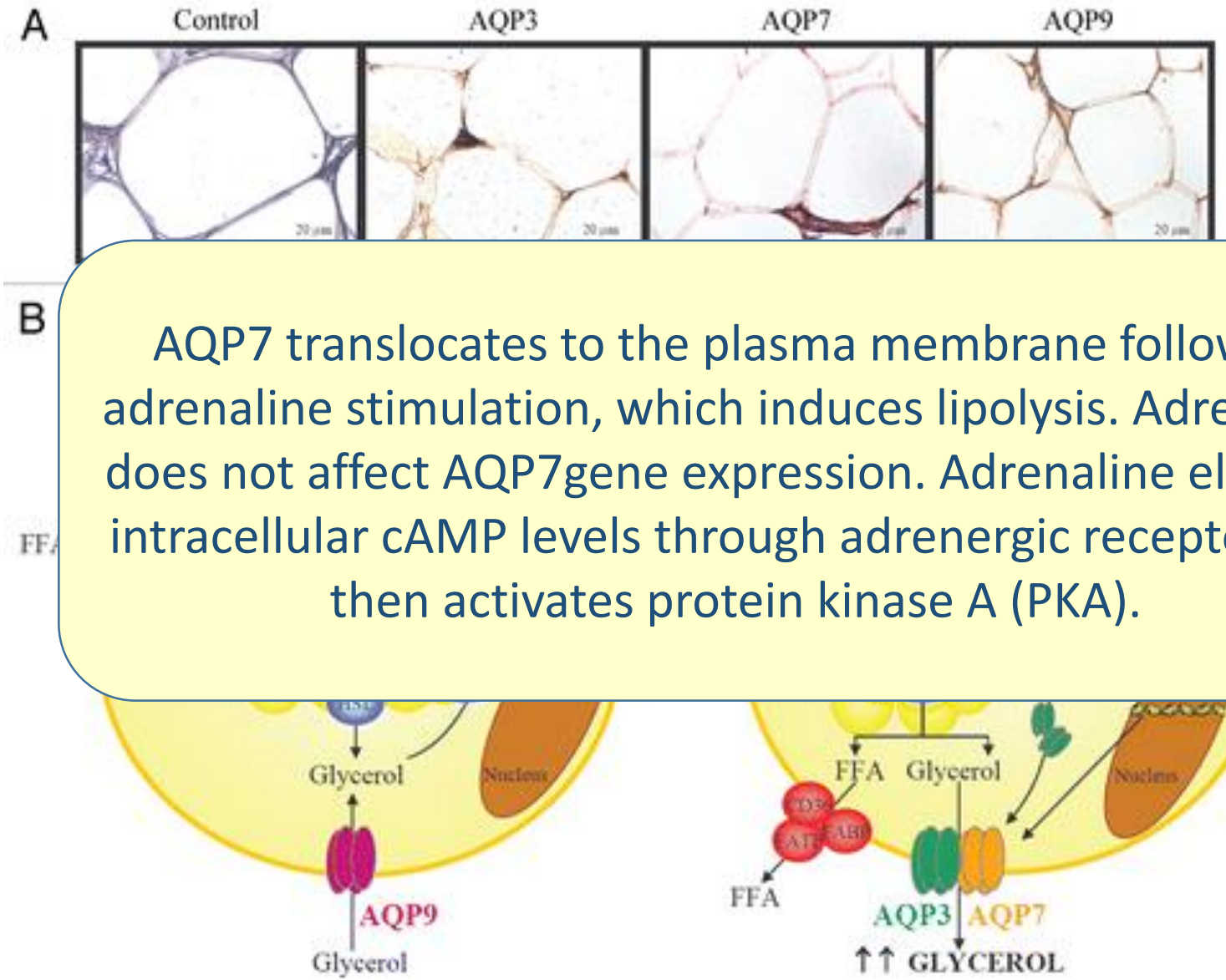
Aquaporin's channel action

Aquaporins	Metabolic Function	Fertility Function
AQP3	Adipocyte glycerol efflux Upregulated by insulin Upregulated by leptin	Sperm osmoadaptation
AQP7	Adipocyte glycerol efflux Upregulated by insulin Downregulated by leptin Increases insulin sensitivity	Sperm motility Spermiogenesis
AQP9	Adipocyte glycerol influx Hepatocyte glycerol influx Upregulated by insulin Downregulated by leptin	Spermatogenesis Regulation of epididymal osmolarity Lactate secretion for germ cells Upregulated by sex hormones

Aquaporin's channel action

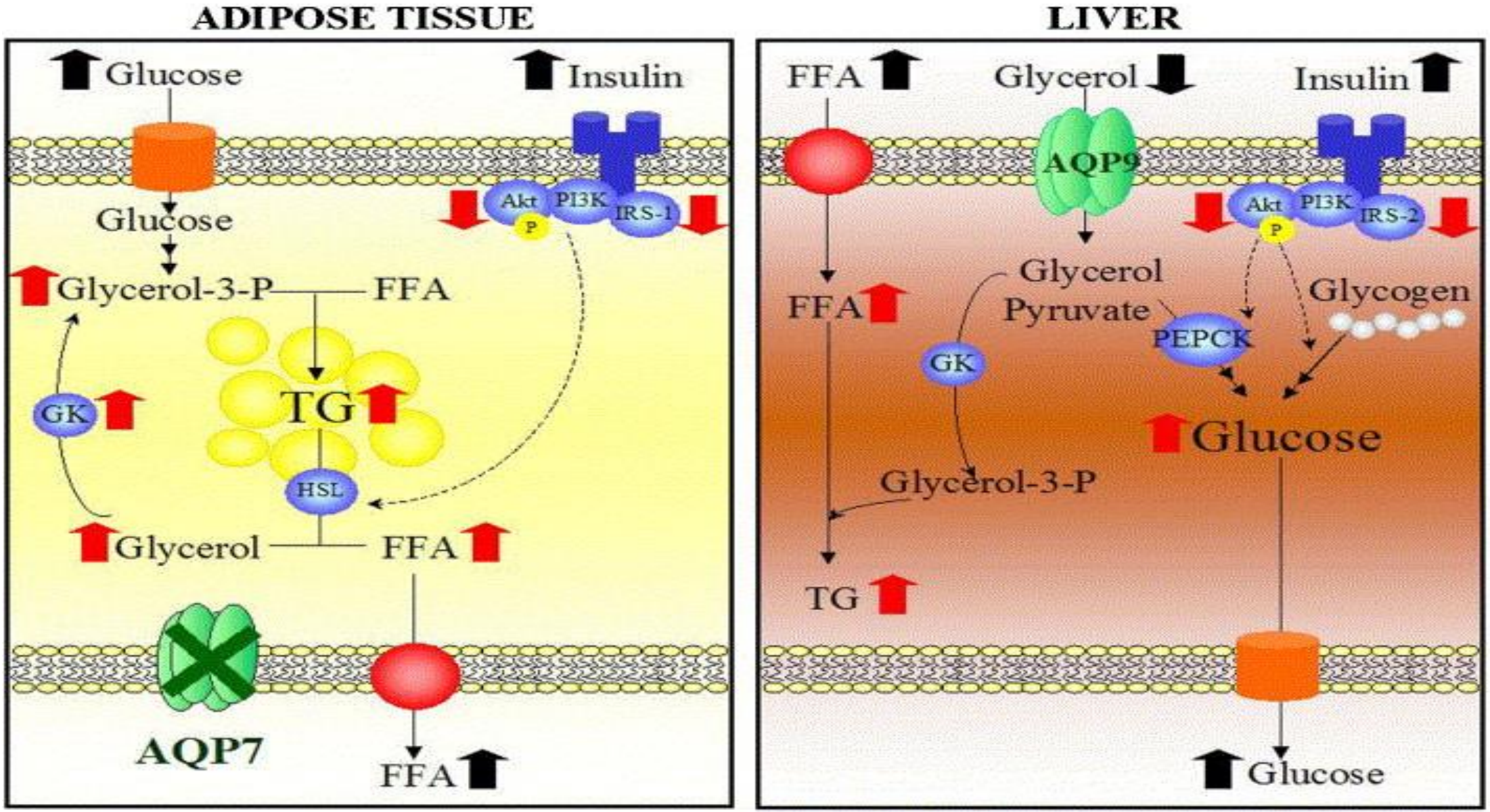


Aquaporin's channel action

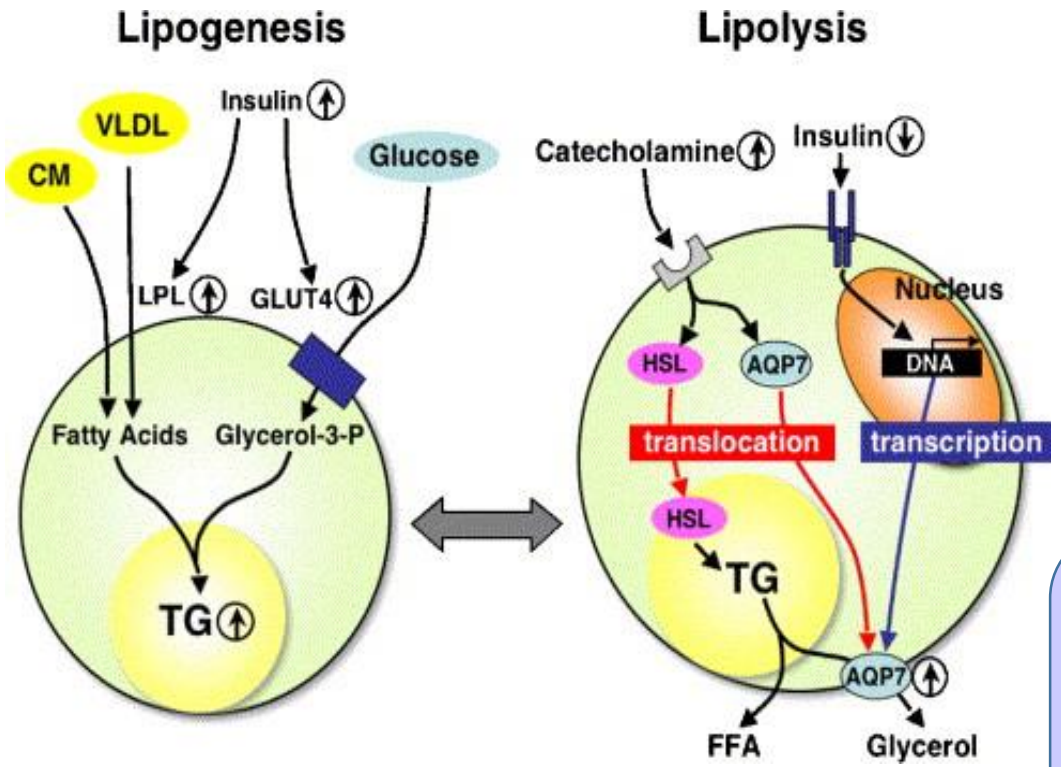


AQP7 translocates to the plasma membrane following adrenaline stimulation, which induces lipolysis. Adrenaline does not affect AQP7gene expression. Adrenaline elevates intracellular cAMP levels through adrenergic receptor and then activates protein kinase A (PKA).

Aquaporin's channel action



Aquaporin's channel action

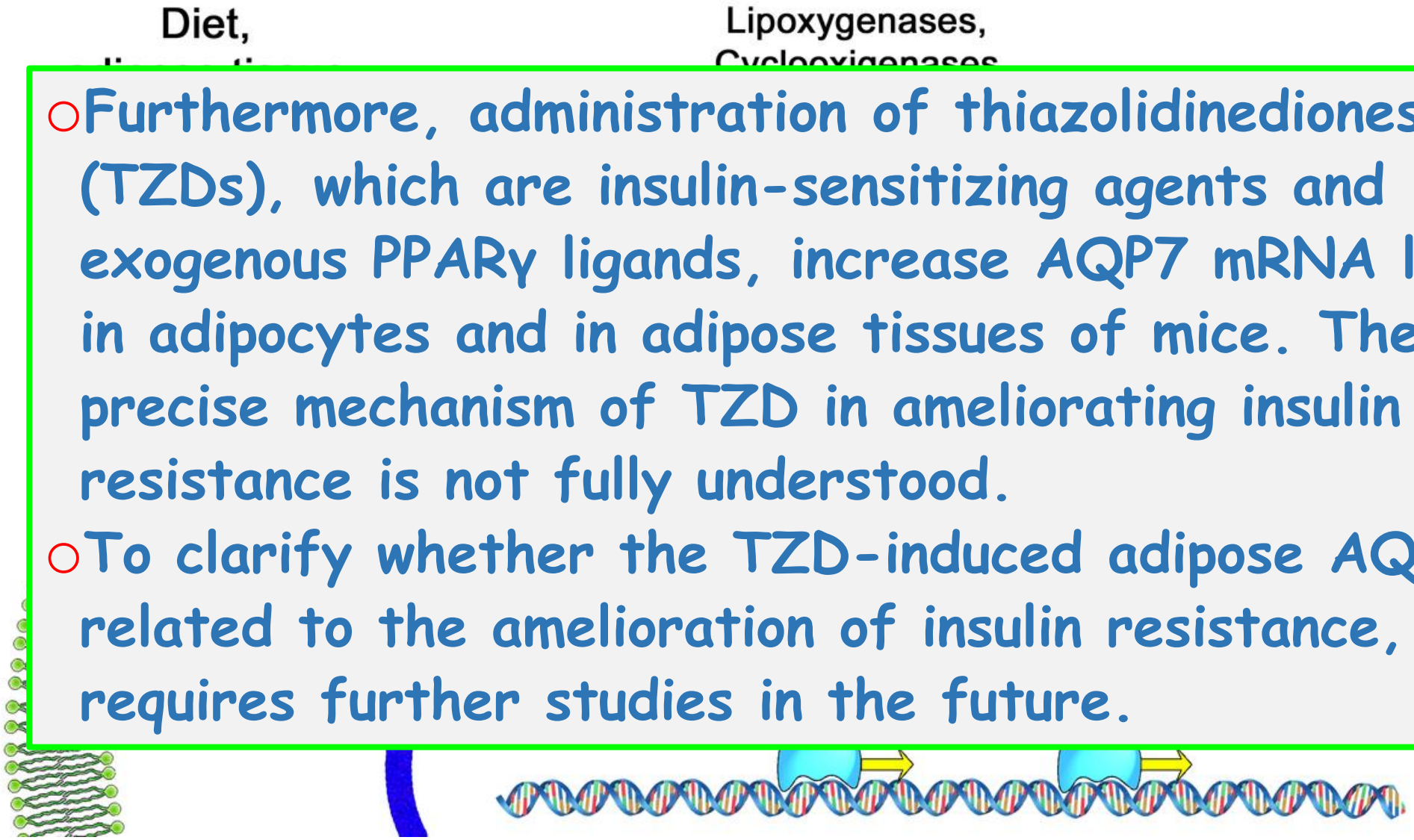


Moreover, AQP7 mRNA levels are elevated by the decrease of insulin signaling cascade. Thus, long-term regulation of AQP7 is under the control of insulin while short-term regulation is under catecholamines.

AQP7 is highly expressed in white adipose tissue (WAT), brown adipose tissue (BAT), and testis. Furthermore, a weak expression of AQP7 is also observed in the heart, skeletal muscles, and kidneys.

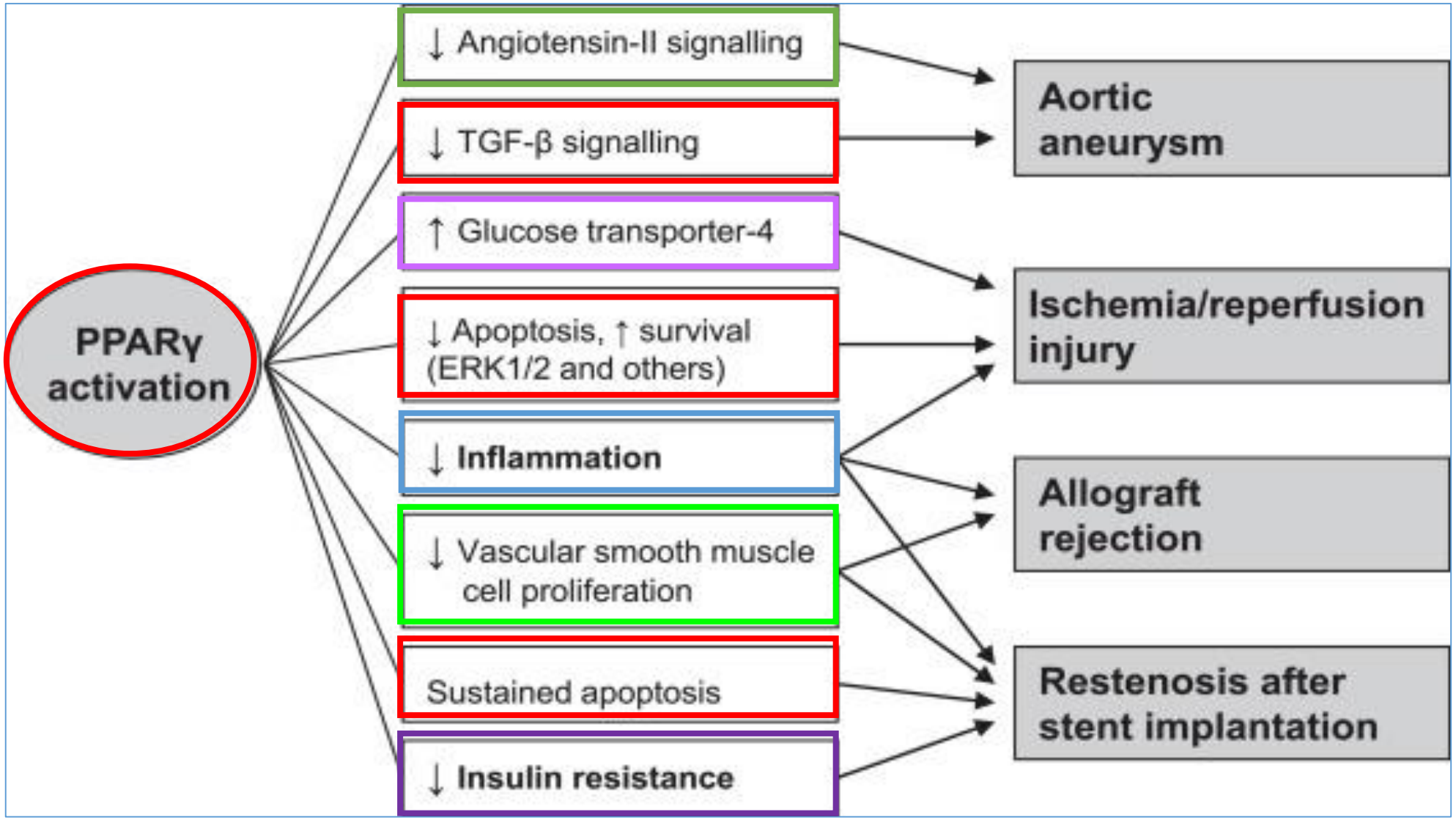
Peroxisome proliferator activated receptor γ (PPARγ) is a master regulator of adipocytes differentiation and regulates several adipose-specific genes at the transcriptional level. PPARγ forms a heterodimer with **retinoic acid X receptor α** (RXRα), and binds to peroxisome proliferator response element (PPRE) site. The PPRE site is identified in the promoter region of AQP7 gene

PPARγ actions

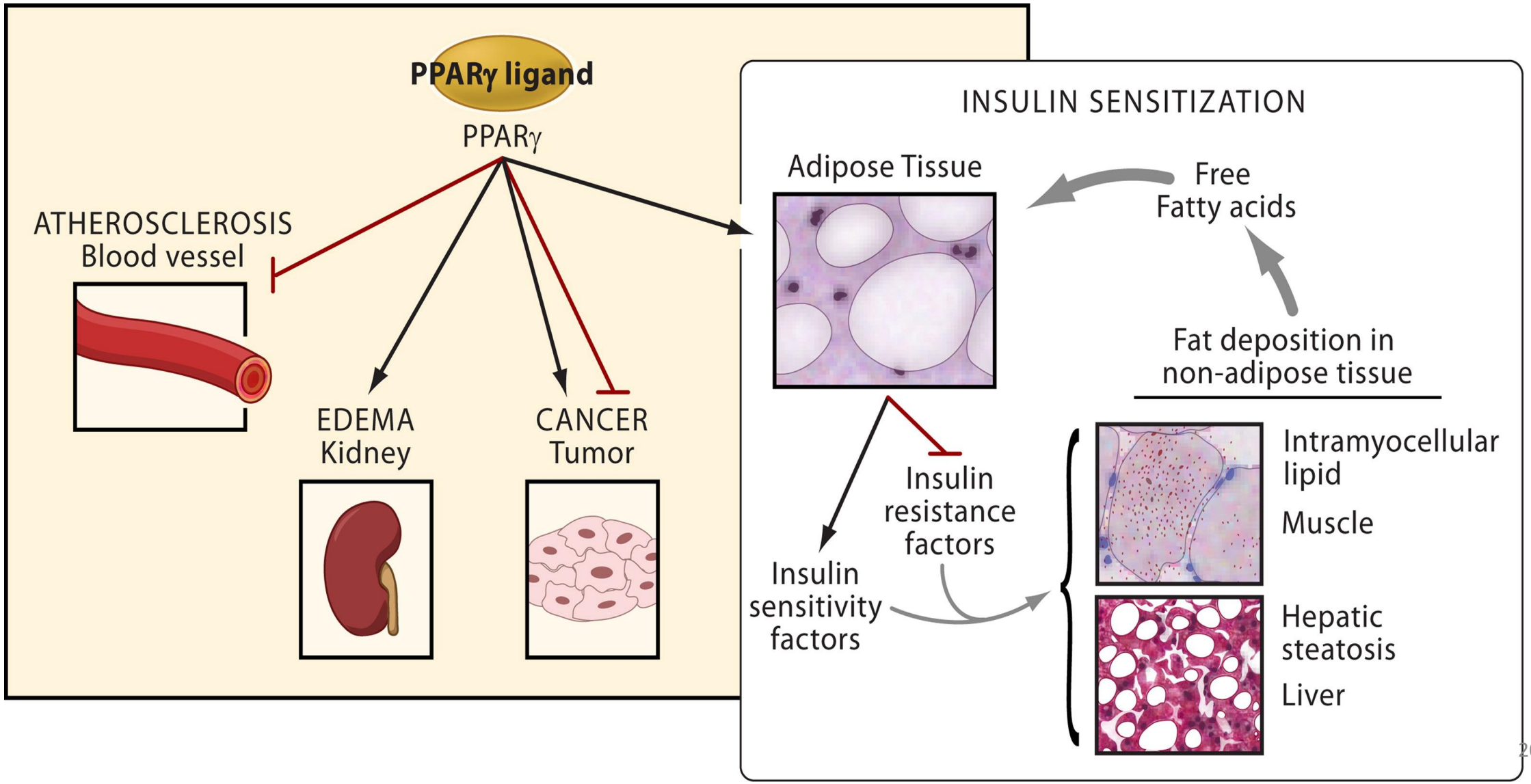


- Furthermore, administration of thiazolidinediones (TZDs), which are insulin-sensitizing agents and exogenous PPARγ ligands, increase AQP7 mRNA levels in adipocytes and in adipose tissues of mice. The precise mechanism of TZD in ameliorating insulin resistance is not fully understood.
- To clarify whether the TZD-induced adipose AQP7 is related to the amelioration of insulin resistance, requires further studies in the future.

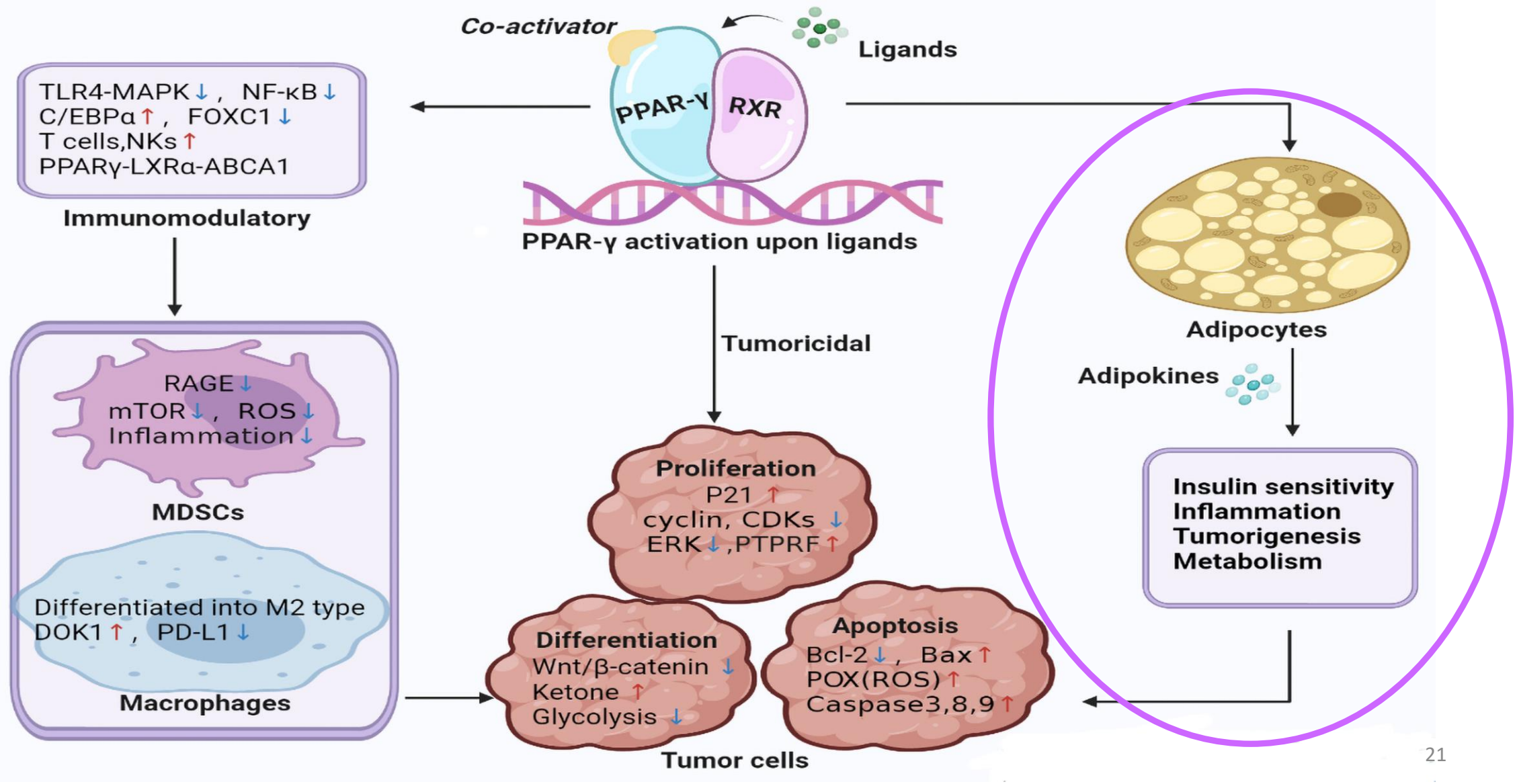
PPARγ actions



PPARγ actions



PPARγ actions



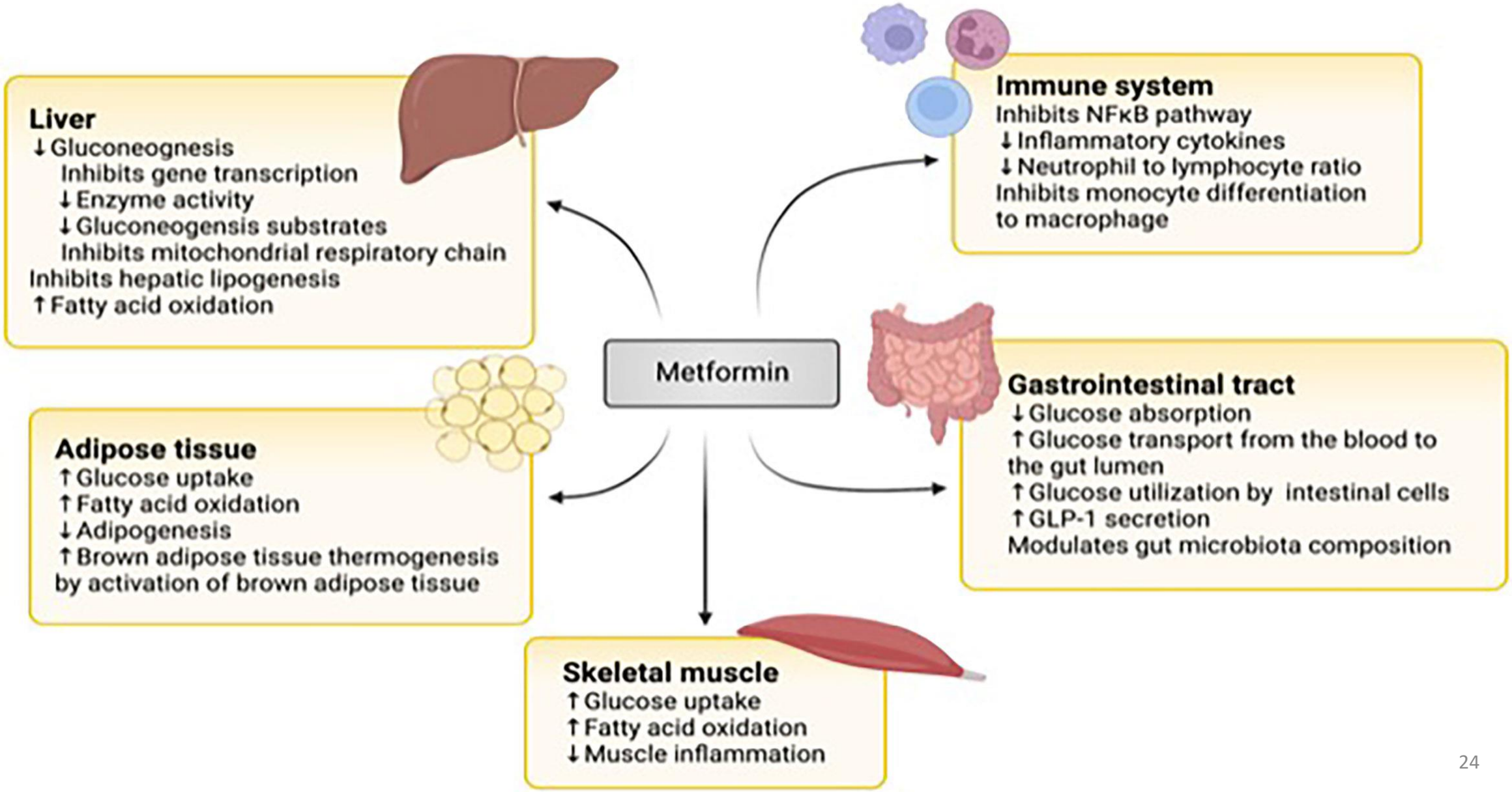
Effect of insulin on aquaporin 7

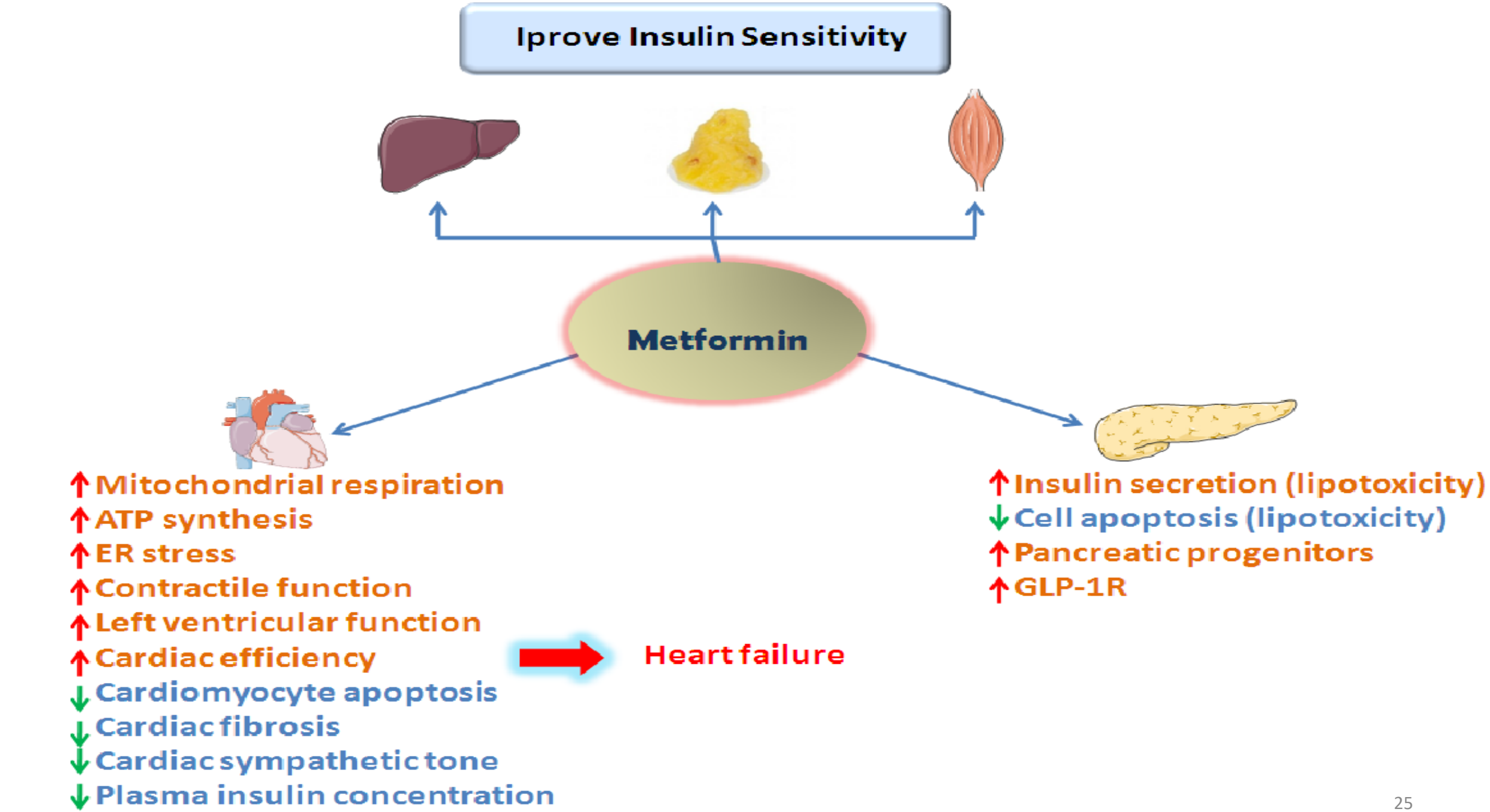
- The **insulin negative response element (IRE)** is identified in the promoter region of AQP7 gene.
- This result indicates that AQP7 mRNA expression is closely regulated by insulin at the transcriptional level. Furthermore, glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), which are key enzymes of gluconeogenesis, also contain IRE in their promoter regions.
- Insulin also suppresses the mRNA levels of G6Pase and PEPCK. Taken together, plasma glycerol levels are partly determined by insulin through adipose AQP7, and suggests that adipose AQP7 may be associated with glucose metabolism.

Metformin

- Metformin is a widely used antidiabetic drug for treating type 2 diabetes mellitus (T2DM) that enhances insulin regulation of glucose, promotes weight loss, and reduces appetite. It reduces insulin resistance and decreases blood glucose concentration by inhibiting gluconeogenesis and suppressing hepatic glucose production.

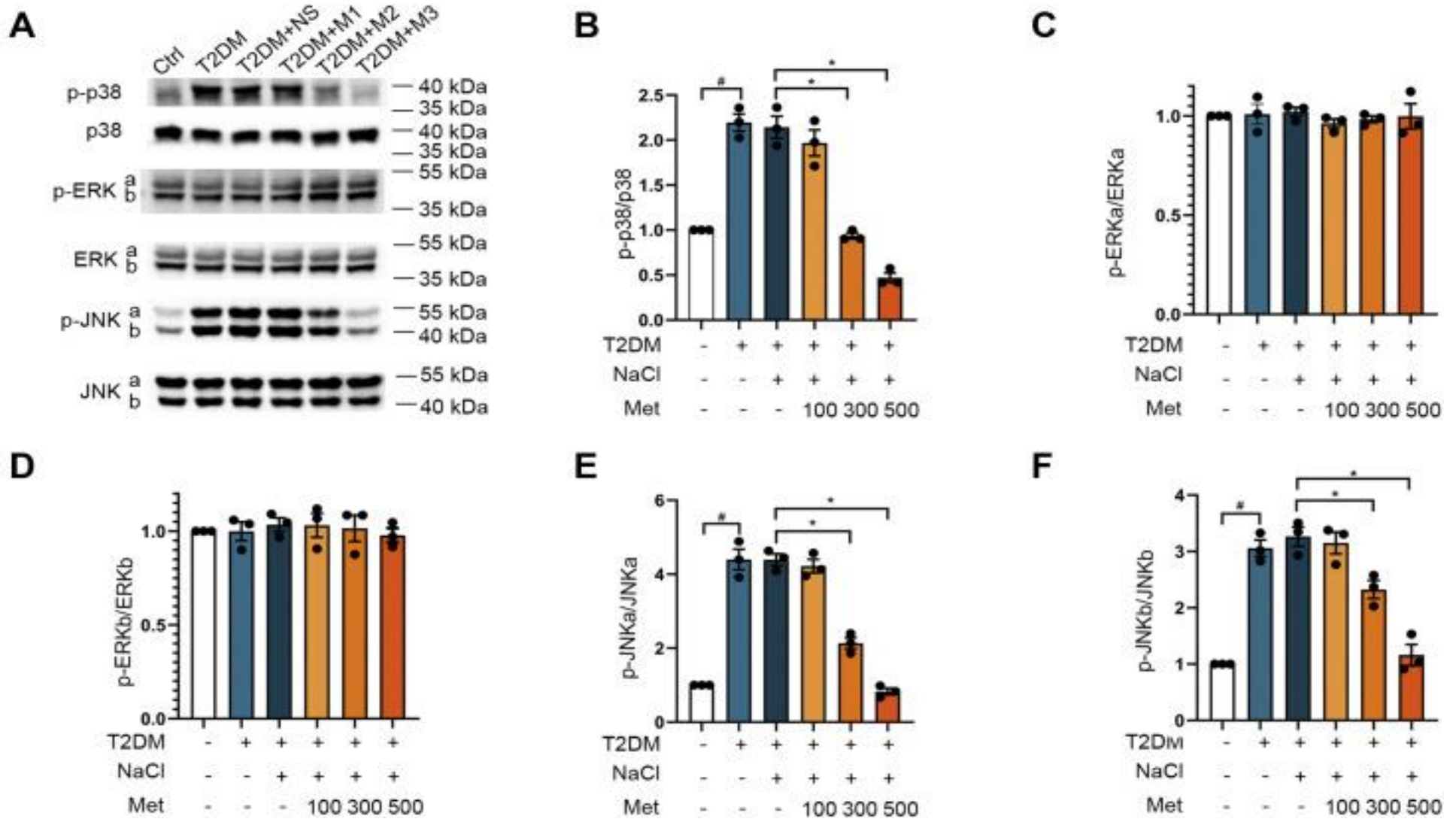
Metformin actions



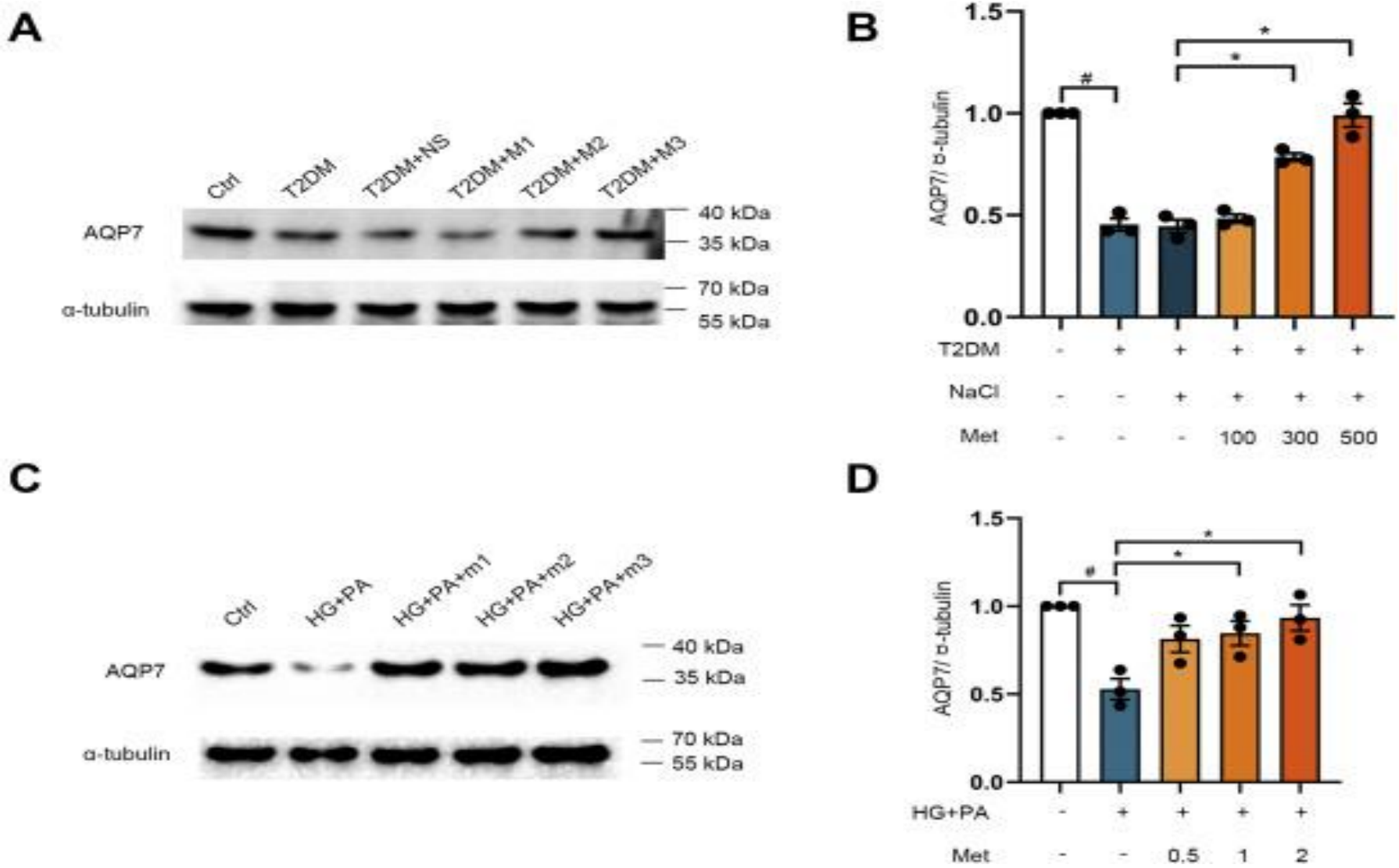

Iprove Insulin Sensitivity
Metformin
↑Mitochondrial respiration
↑ATP synthesis
↑ER stress
↑Contractile function
↑Left ventricular function
↑Cardiac efficiency
↓Cardiomyocyte apoptosis
↓Cardiac fibrosis
↓Cardiac sympathetic tone
↓Plasma insulin concentration
Heart failure
↑Insulin secretion (lipotoxicity)
↓Cell apoptosis (lipotoxicity)
↑Pancreatic progenitors
↑GLP-1R

- Pancreatic β-cell injury and insulin resistance appear to be partially triggered by **inflammatory**, **oxidative**, and **endoplasmic reticulum stress-induced pathways**, including the mitogen-activated protein kinases **(MAPK) signaling cascade**. However, whether MAPK modulations affect AQP7 expression in pancreatic tissue of T2DM treated with metformin remains poorly understood.

Effect of Metformin on JNK pathway

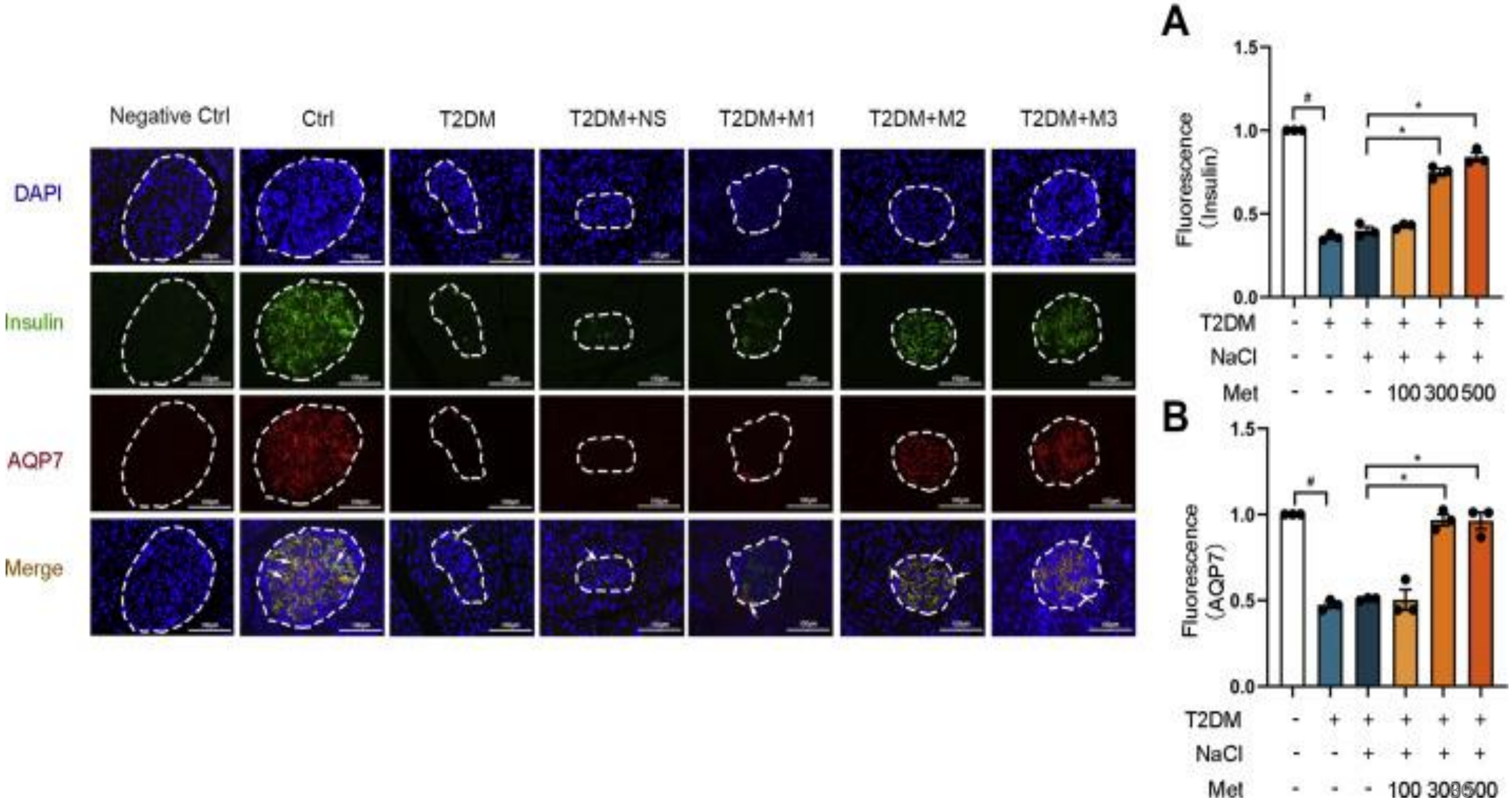


Aquaporin's channel gene expression by Metformin

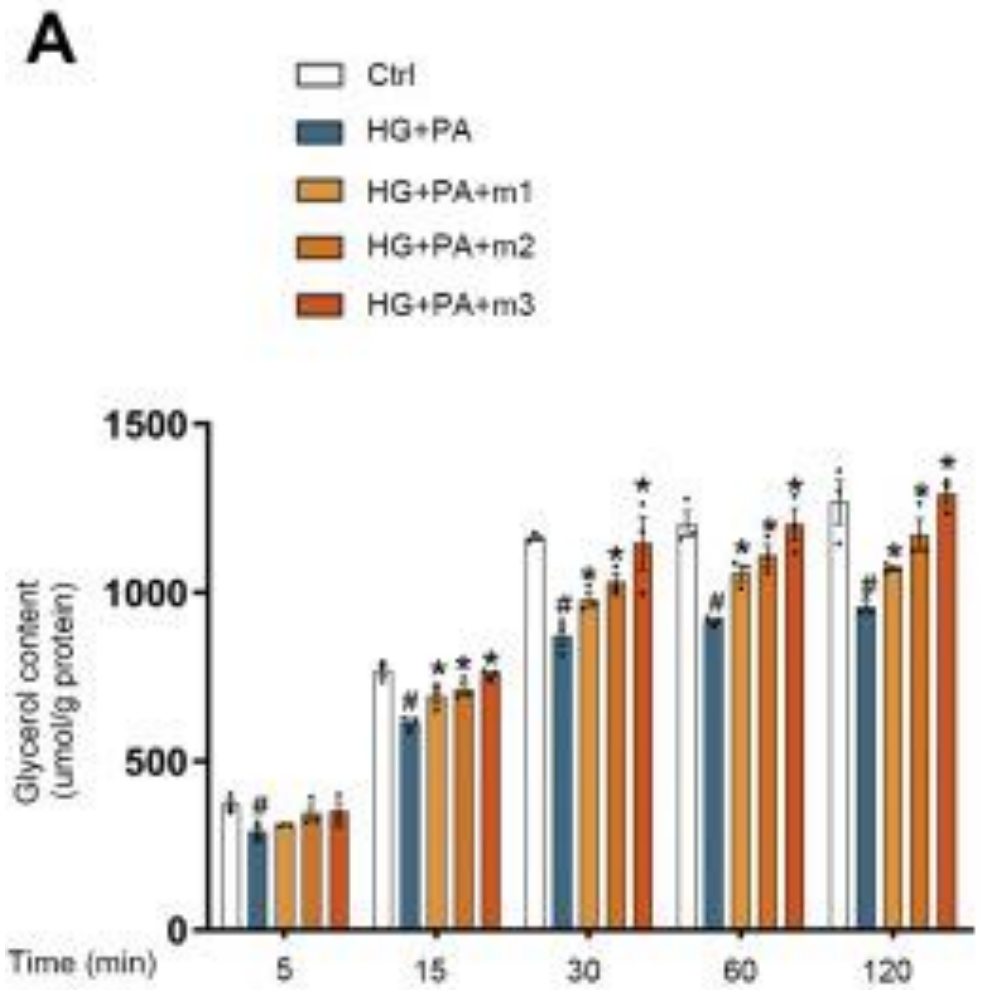


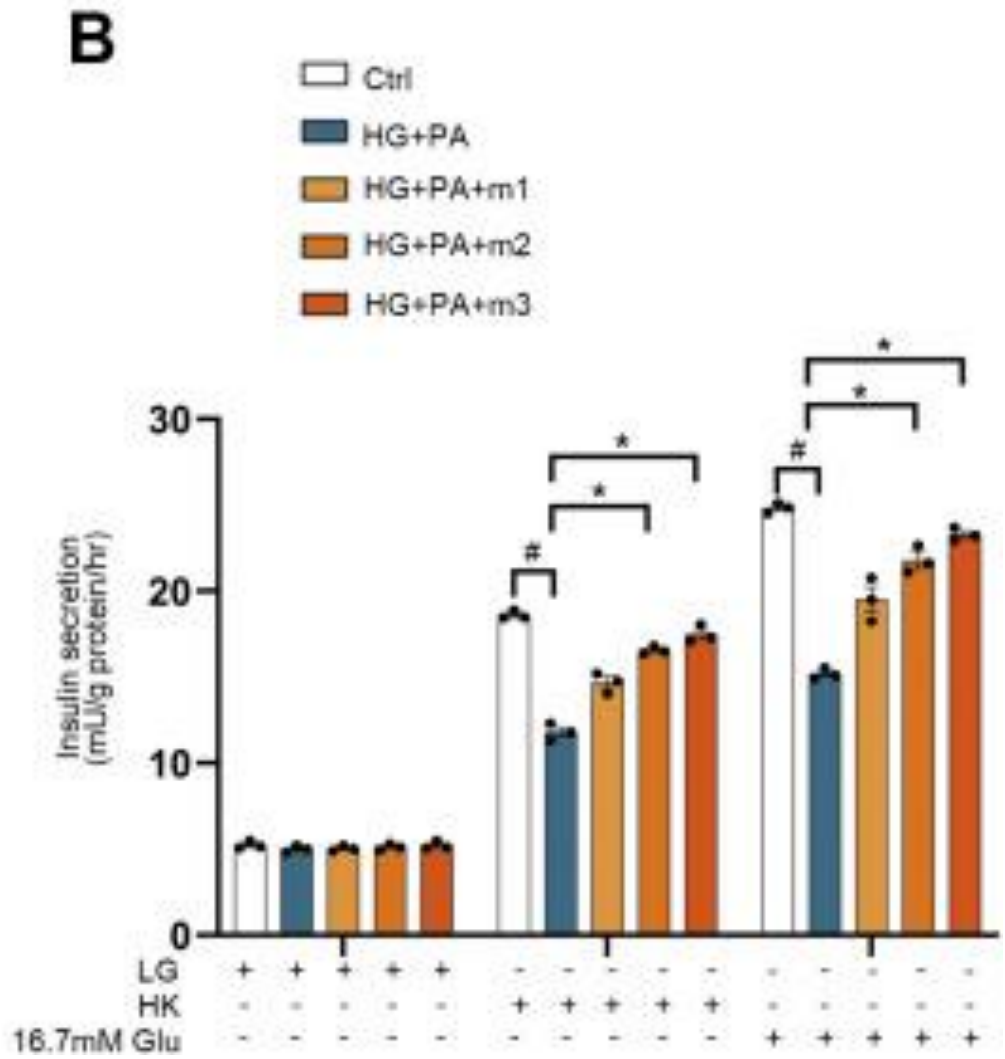
Palmitate

Aquaporin's channel gene expression

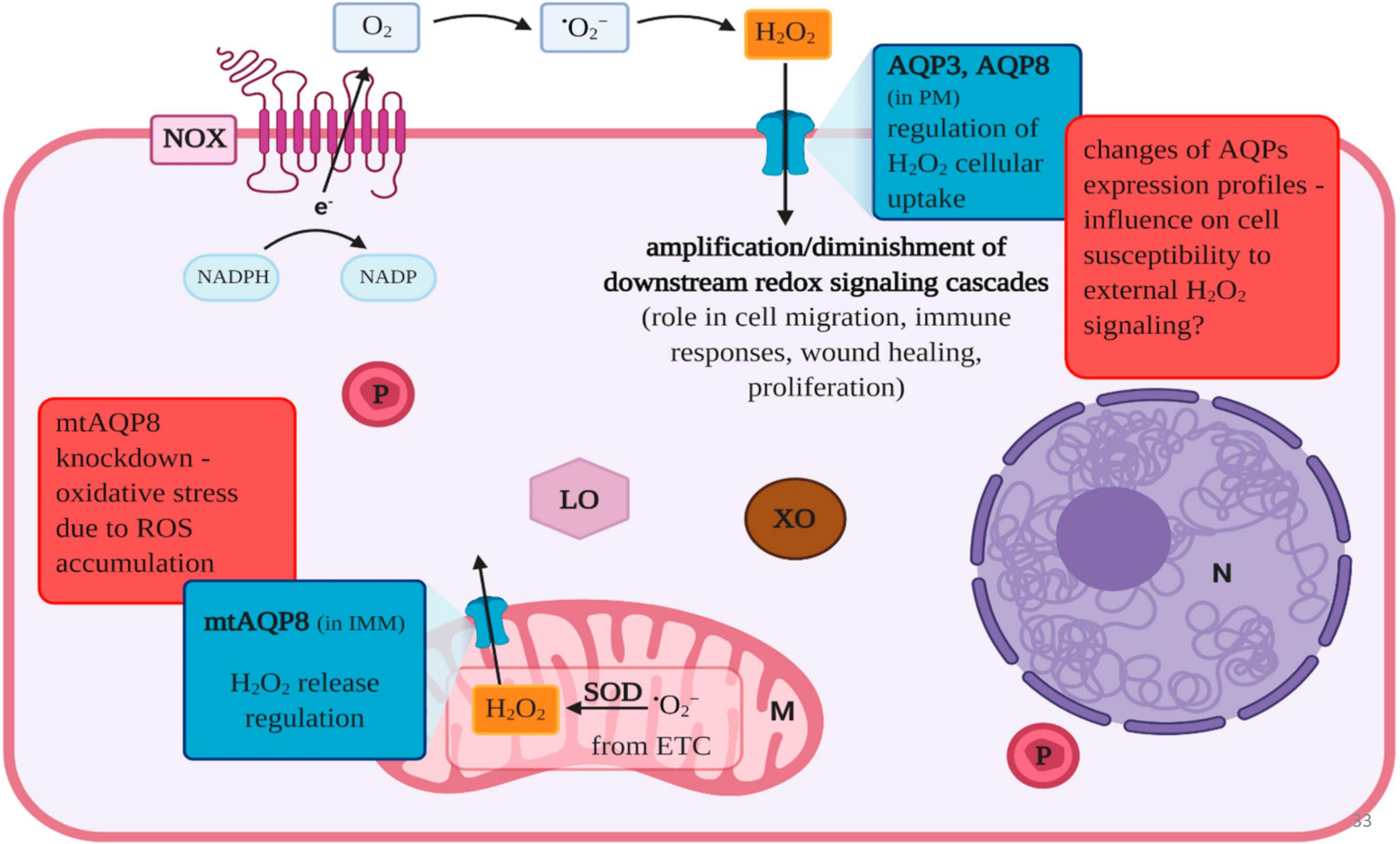


Aquaporin's channel and insulin secretion

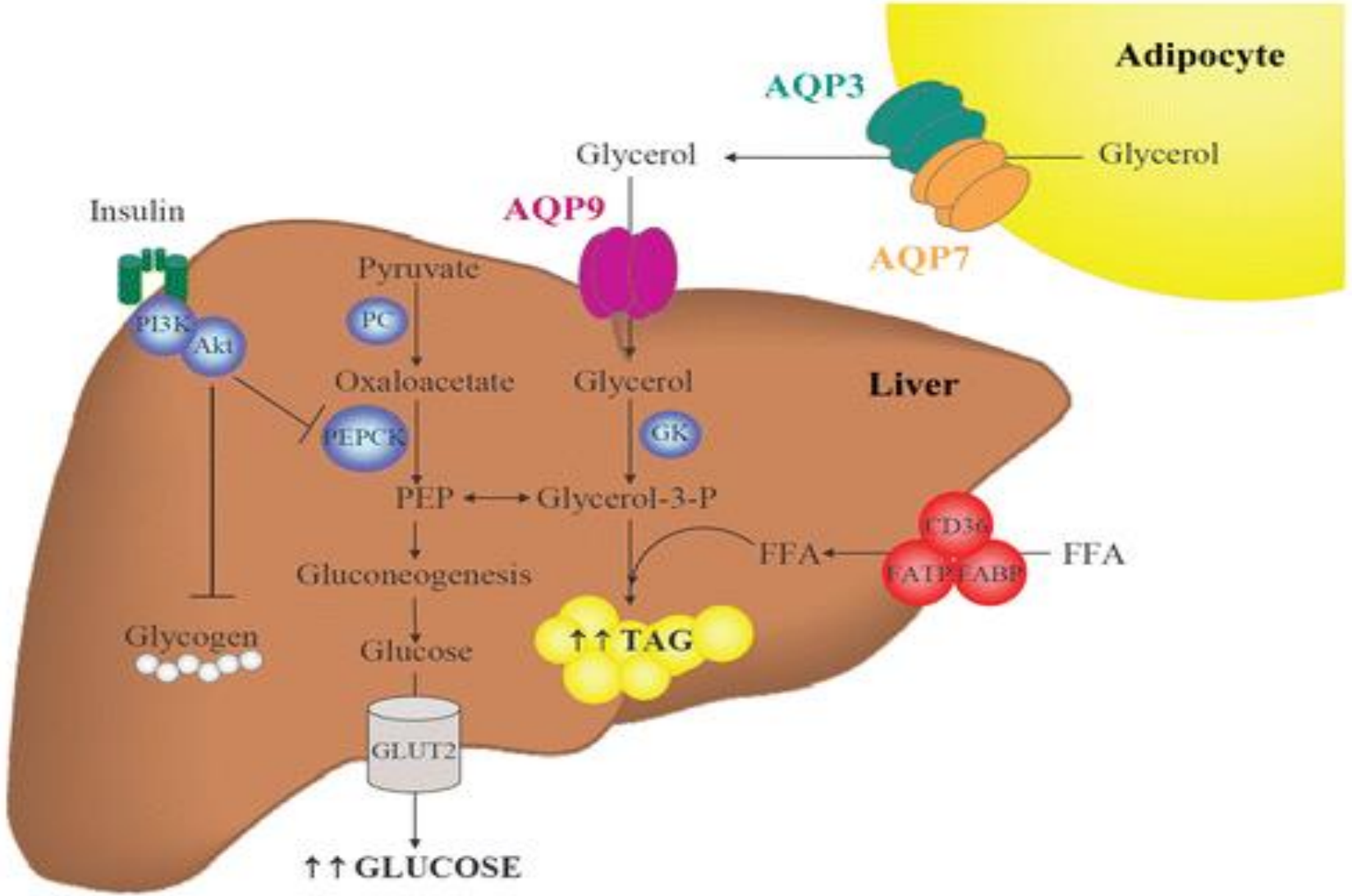




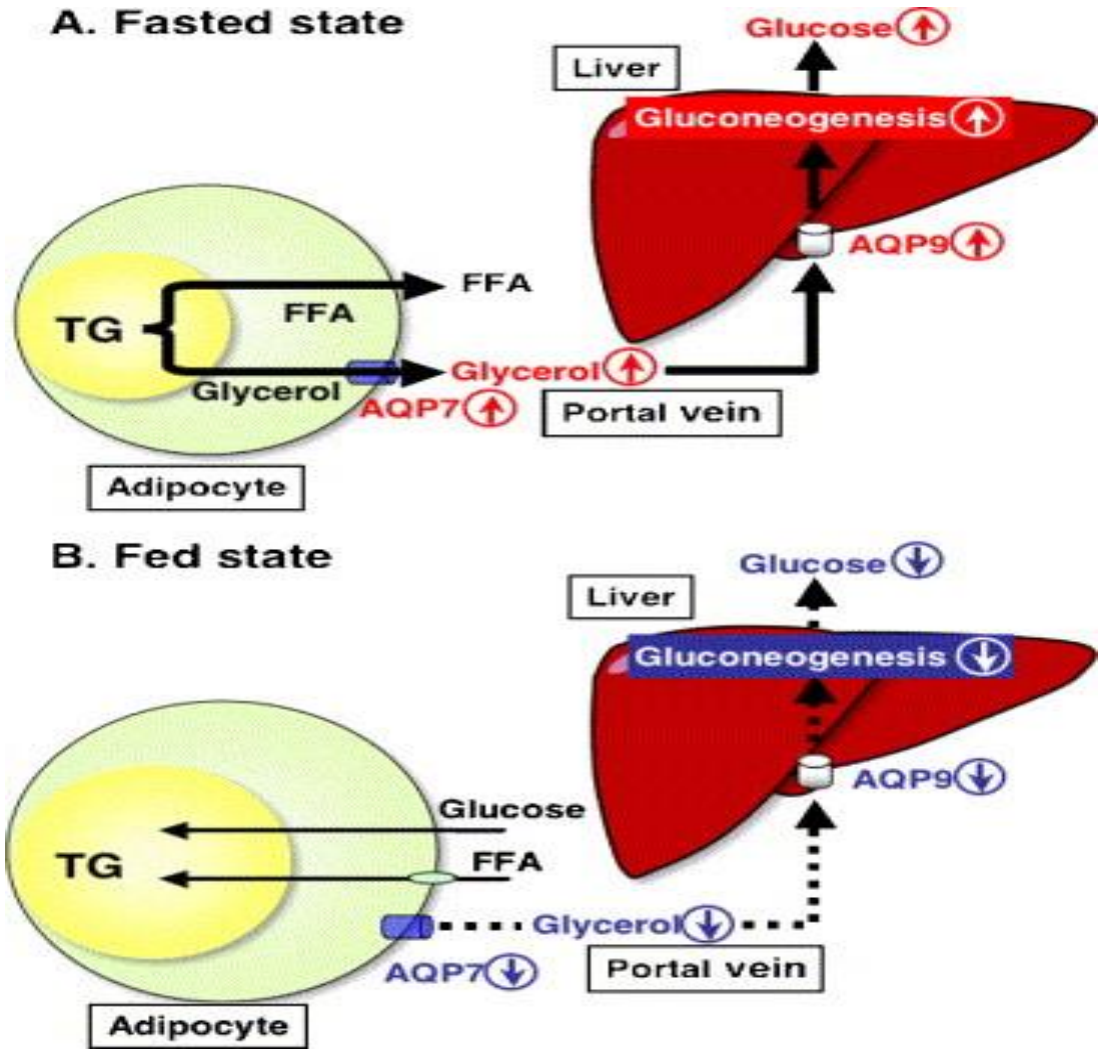
کدامیک در حال تقلب است؟


O_2
$\cdot O_2^-$
H_2O_2
NOX
e^-
NADPH
NADP
AQP3, AQP8
(in PM)
regulation of H_2O_2 cellular uptake
changes of AQPs expression profiles - influence on cell susceptibility to external H_2O_2 signaling?
amplification/diminishment of downstream redox signaling cascades
(role in cell migration, immune responses, wound healing, proliferation)
P
mtAQP8 knockdown - oxidative stress due to ROS accumulation
LO
XO
mtAQP8 (in IMM)
H_2O_2 release regulation
H_2O_2
SOD
$\cdot O_2^-$
from ETC
M
N
P

Aquaporin's channel action



Aquaporin's channel action

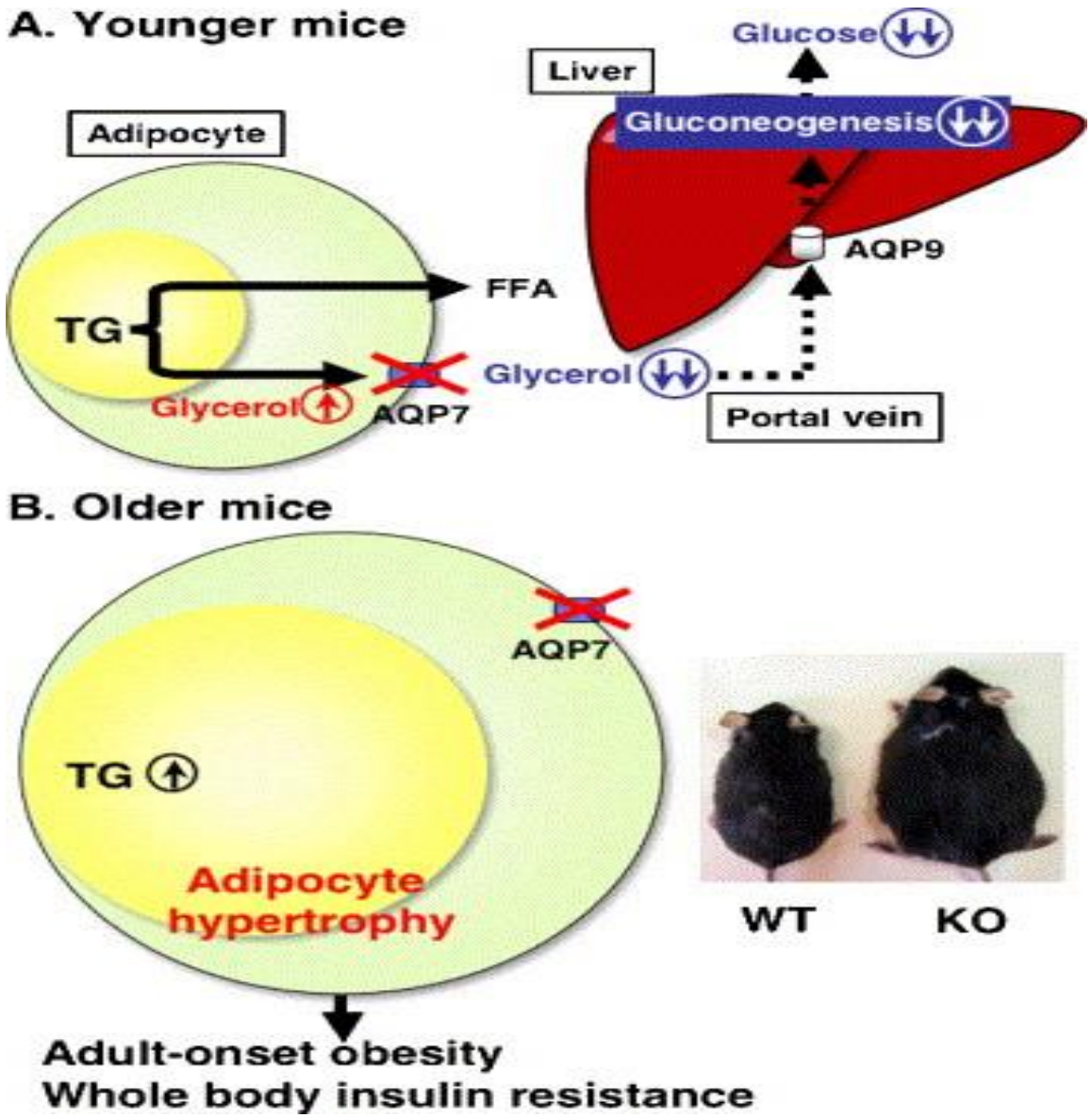


- AQP7 mRNA levels are reduced by feeding and increased by fasting in parallel with plasma glycerol levels.

- These nutrition-related changes in AQP7 and plasma glycerol are the opposites of plasma insulin levels.

- In fact, in adipocytes, insulin suppresses AQP7 mRNA levels in a dose- and time-dependent manners.

Aquaporin's channel action



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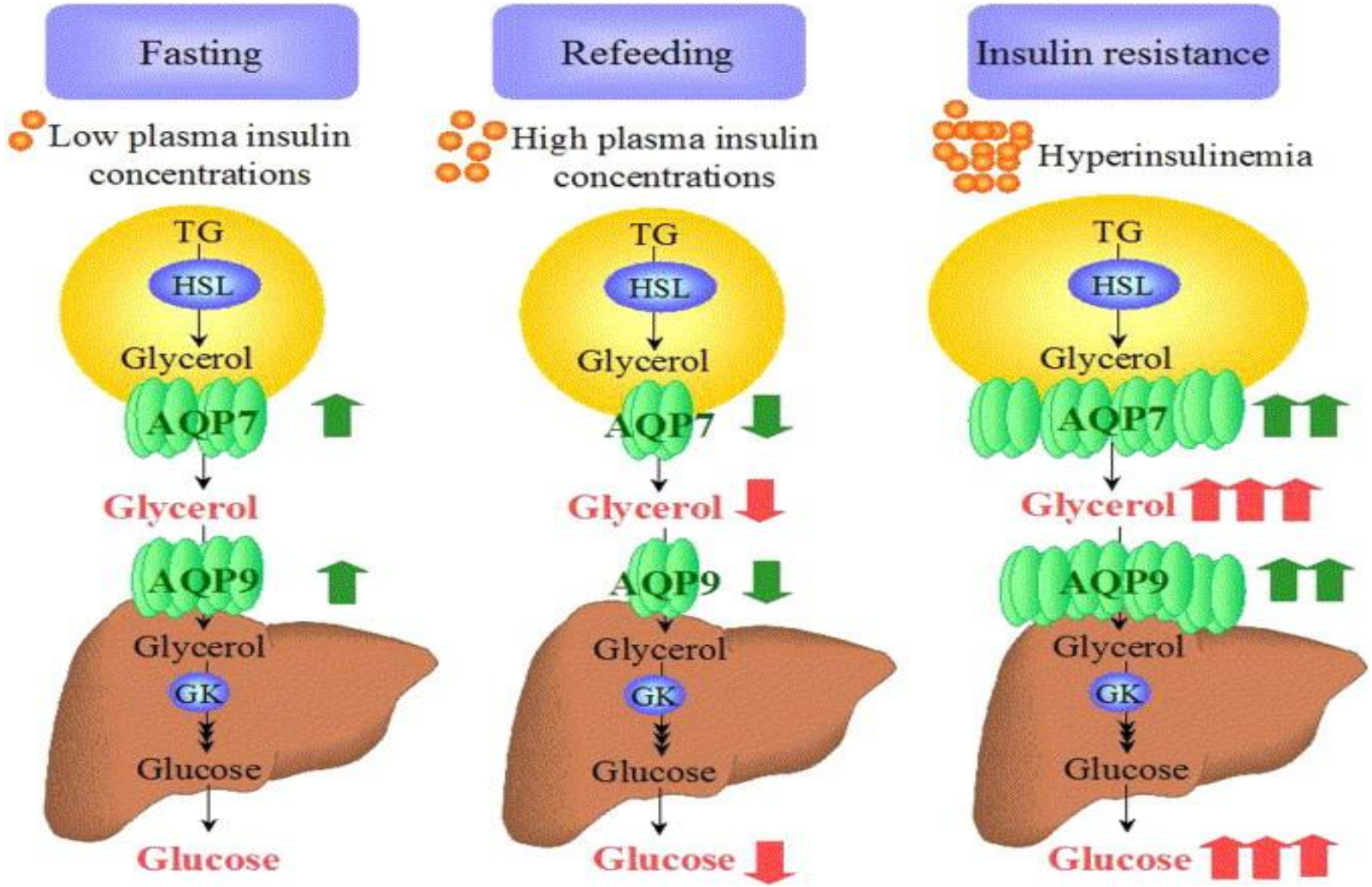
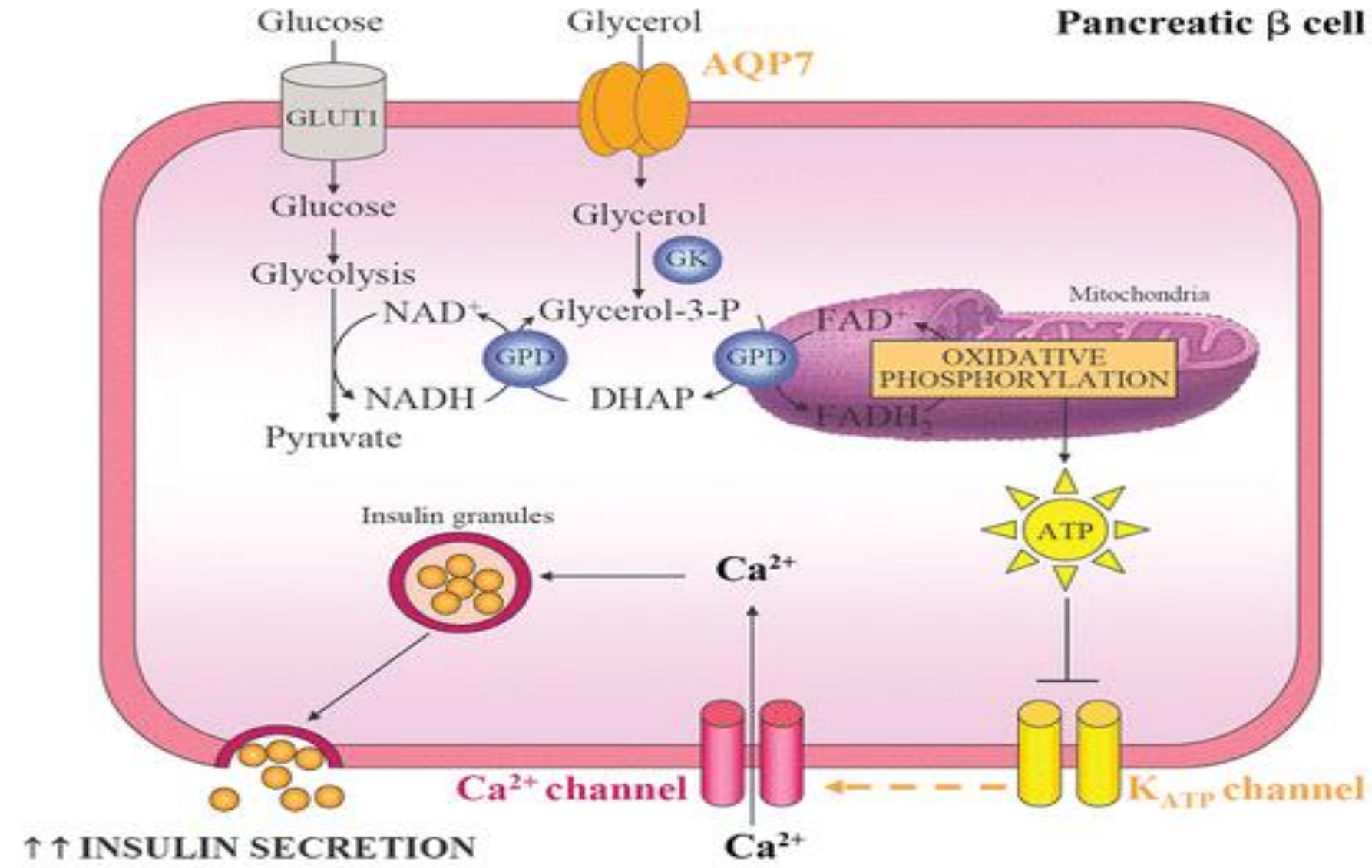


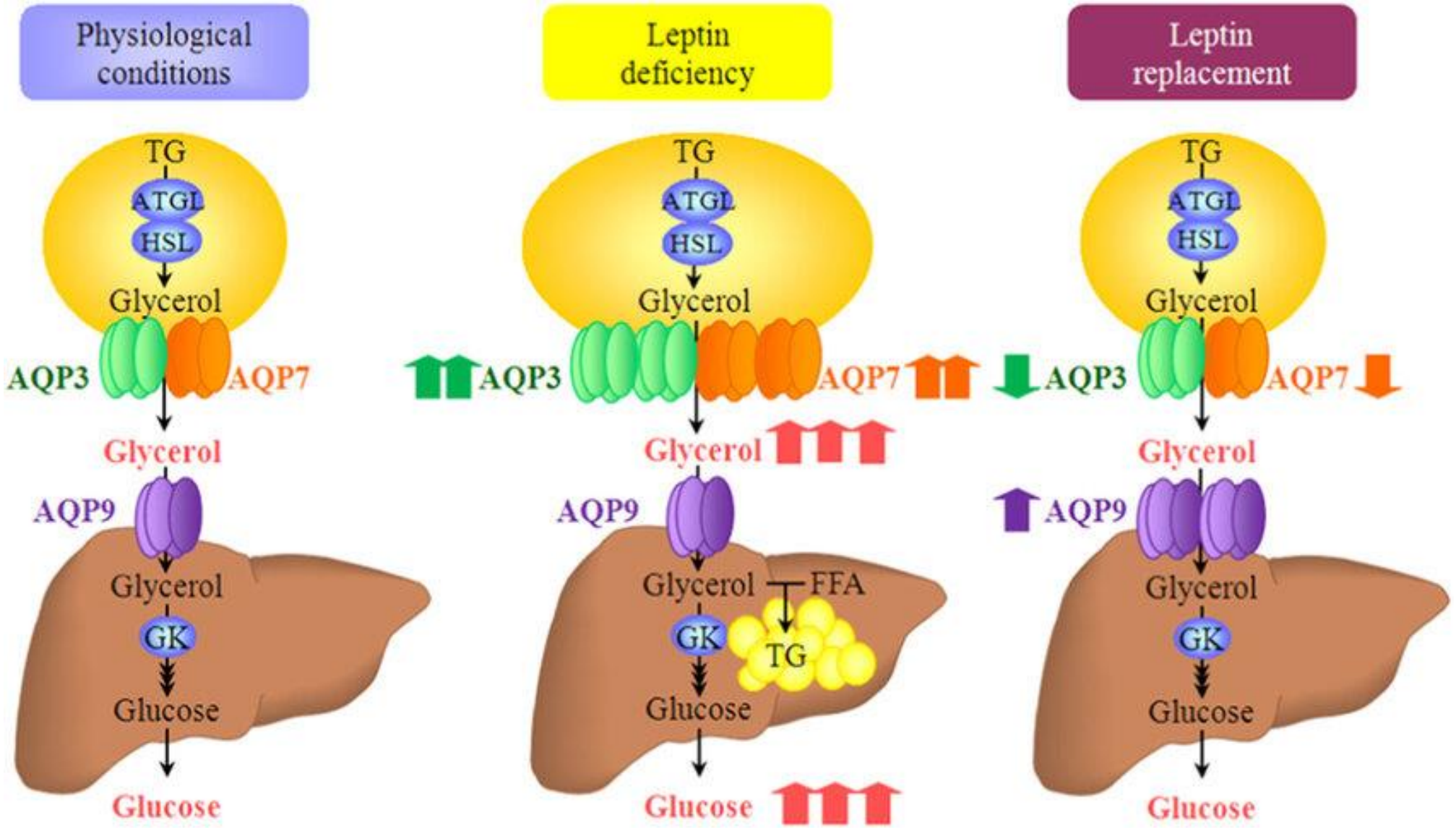
Aquaporin's channel action



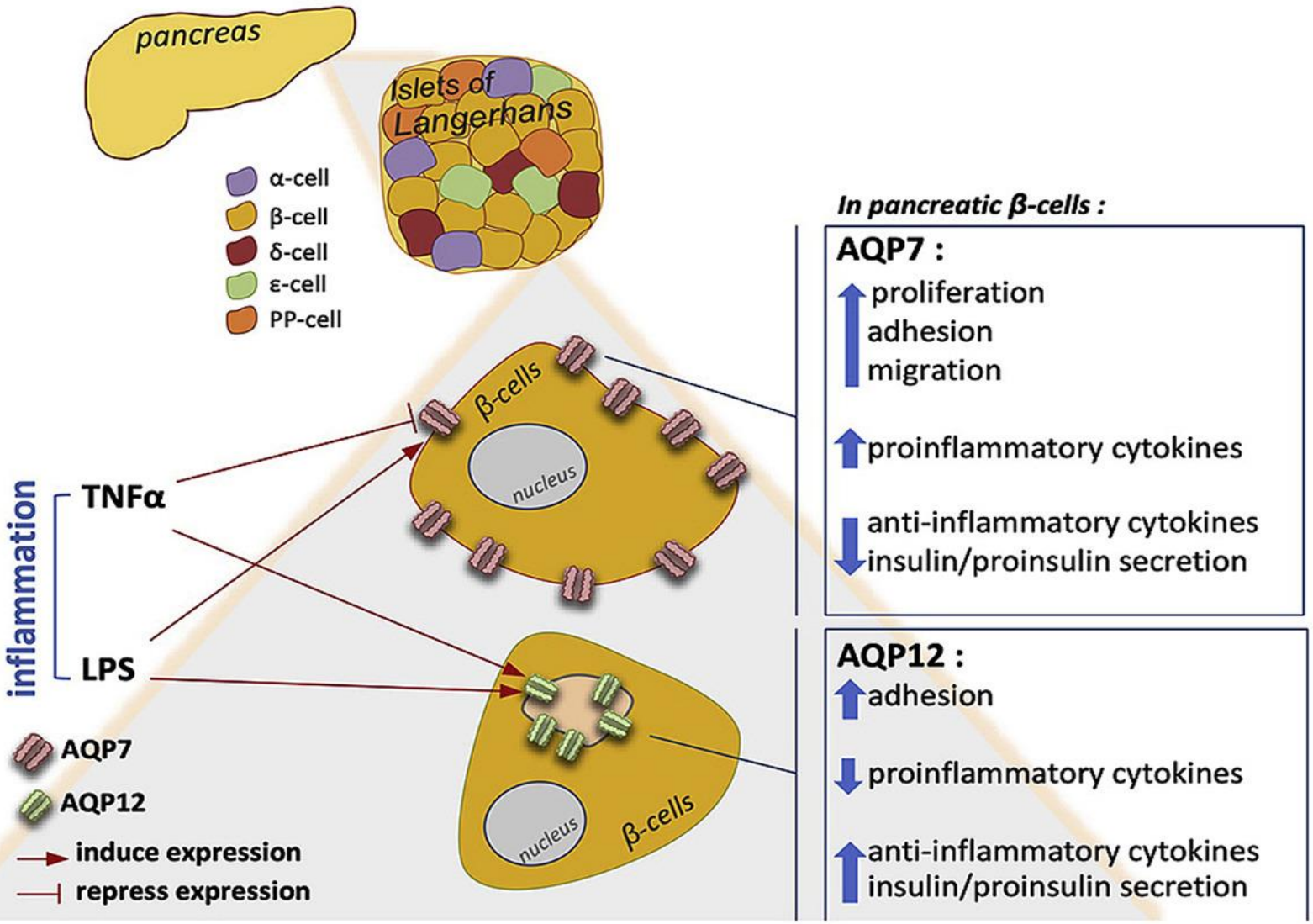
Endocrine pancreas

Sleeve gastrectomy was associated with an upregulation of AQP7 together with a normalization of the increased AQP12 levels in the rat pancreas. Interestingly, ghrelin and GLP-1 repressed AQP7 and AQP12 expression in RIN-m5F β-cells. AQP7 protein was negatively correlated with intracellular lipid accumulation in acylated ghrelin-treated cells and with insulin release in GLP-1-stimulated β-cells.

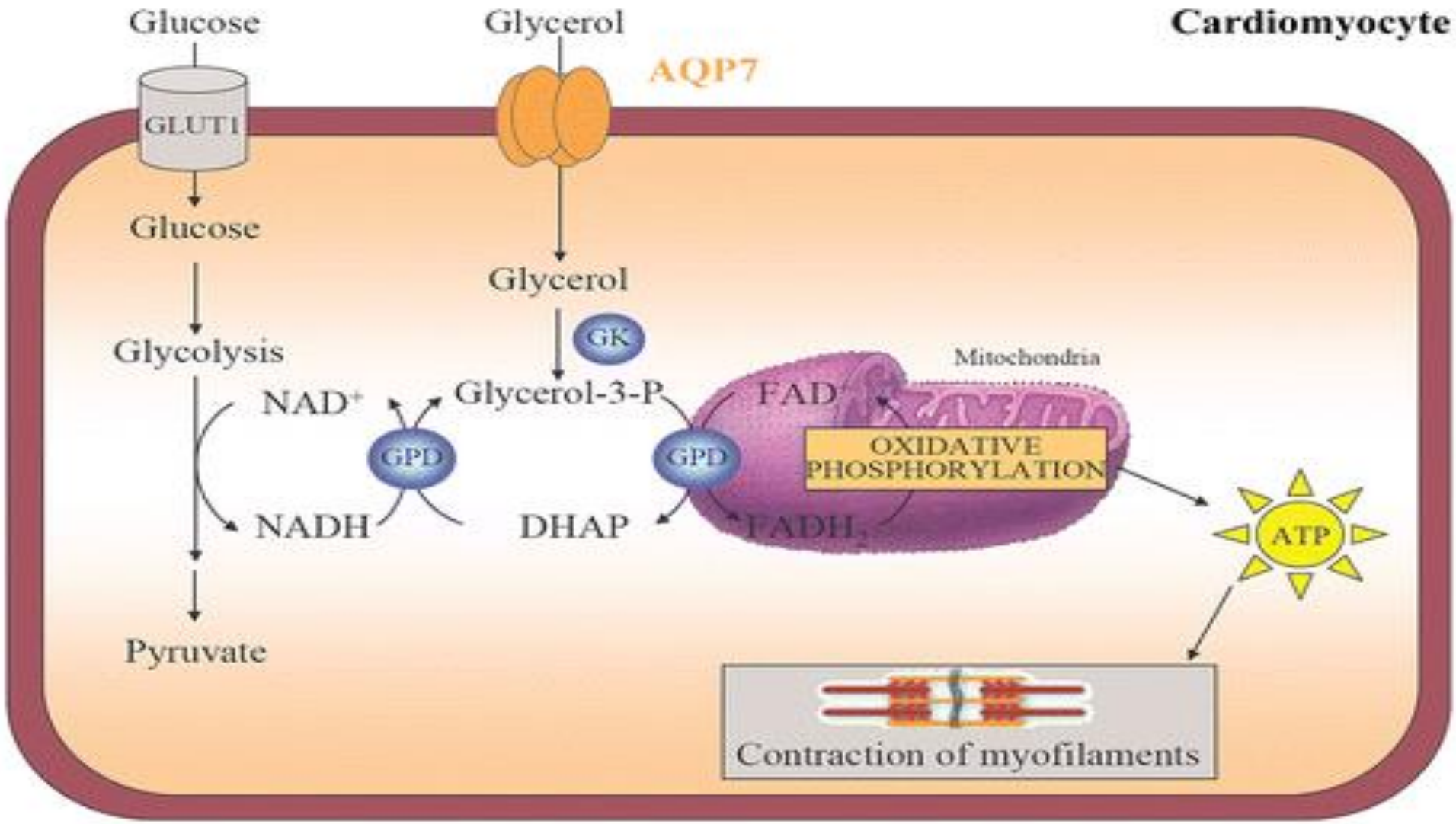
Effect of leptin on Aquaporin's channel



Aquaporin's channel action



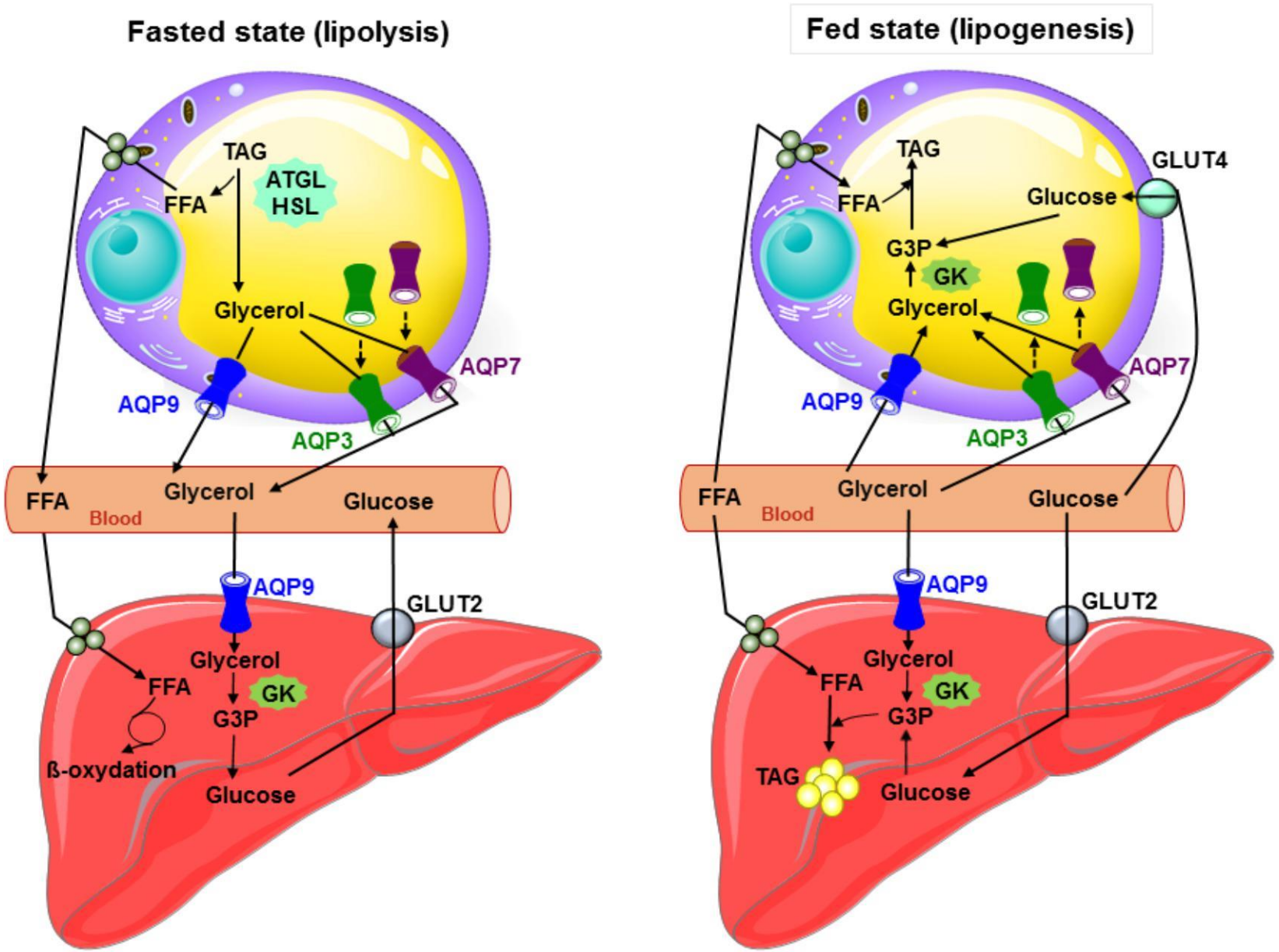
Aquaporin's channel action



Effect of insulin on aquaporin 9

- Insulin suppresses AQP9 mRNA levels in time- and dose-dependent manners in H4IIE hepatocytes.
- Promoter analysis demonstrates that insulin reduces AQP9 mRNA via IRE locating at –496/–502 promoter region.
- Administration of STZ results in increased AQP9 mRNA and protein levels in insulin-insufficient mice.

Aquaporin's channel action

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