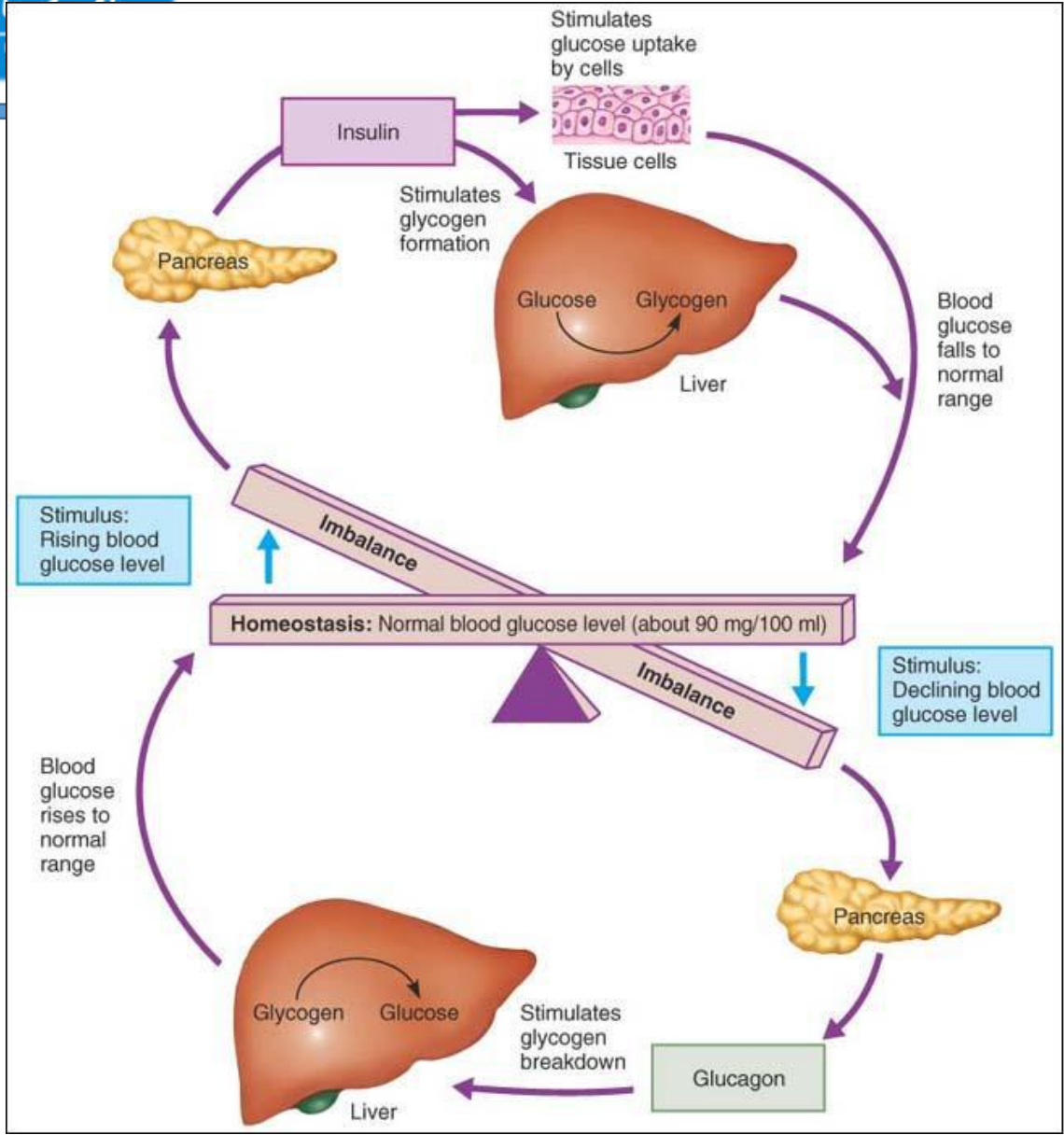




FGF21 Maintains Glucose Homeostasis by Mediating the Cross Talk Between Liver and Brain During Prolonged Fasting

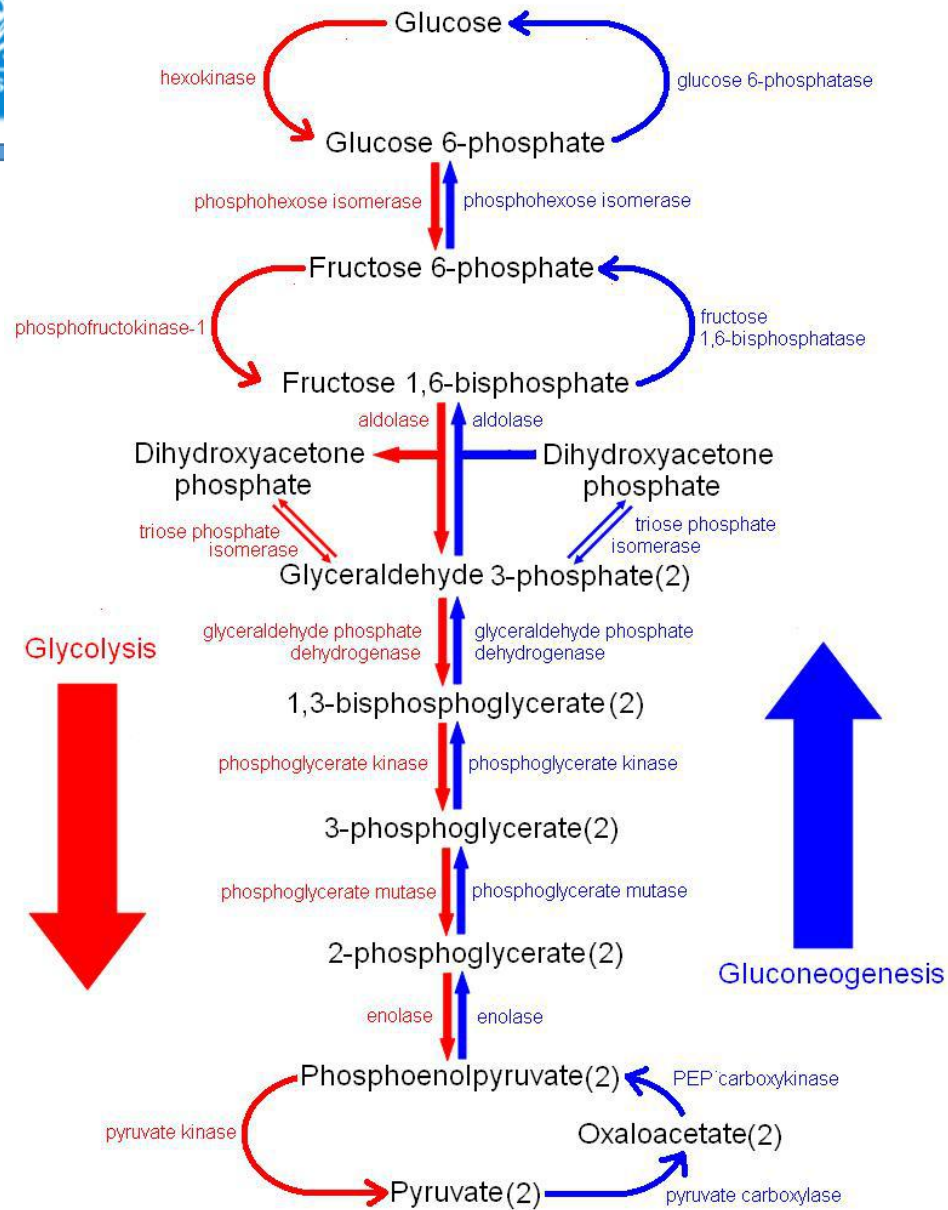
杨丽萍 2017.0319





glucagon,
cortisol,
and insulin

G6Pase



PEPCK

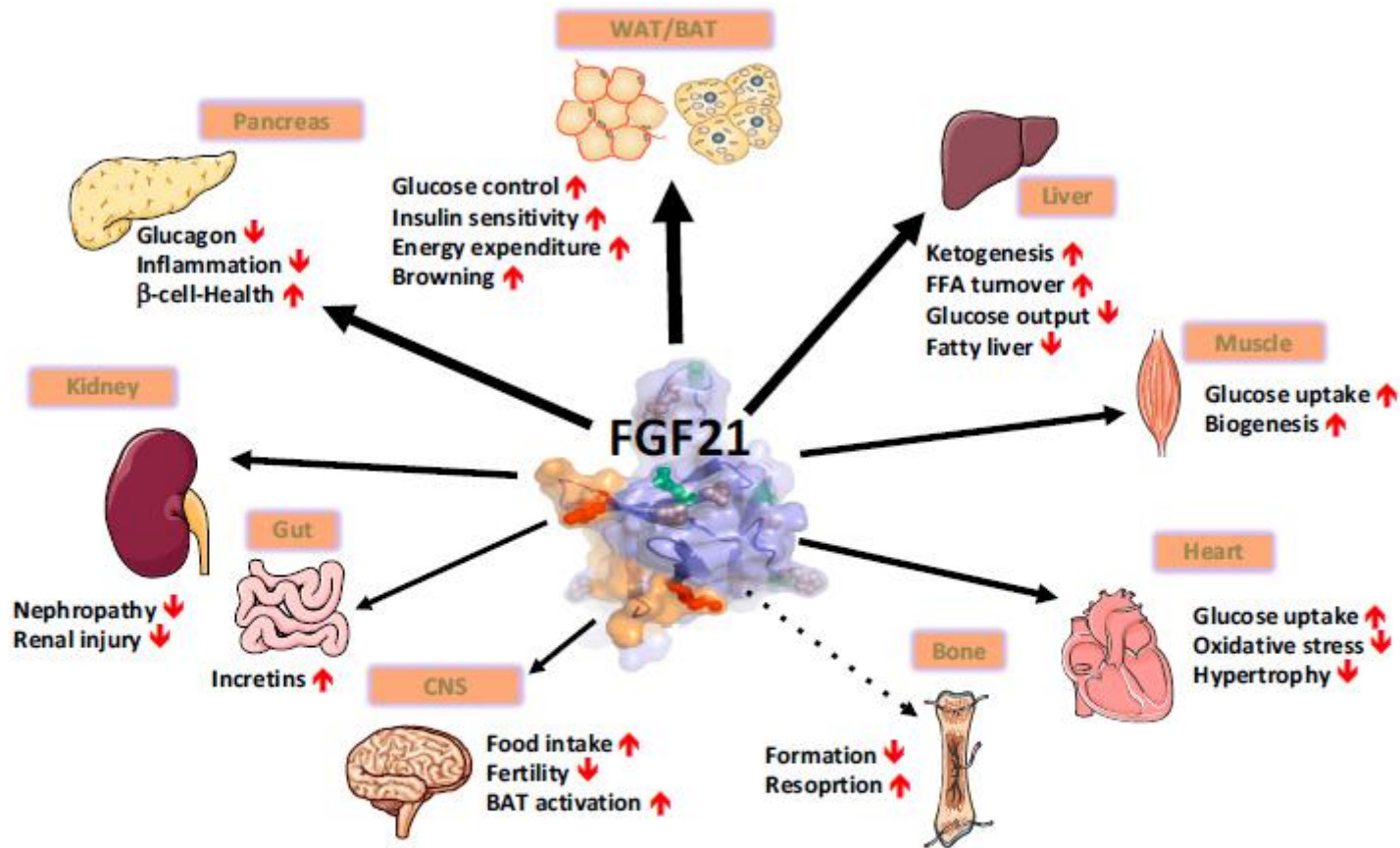
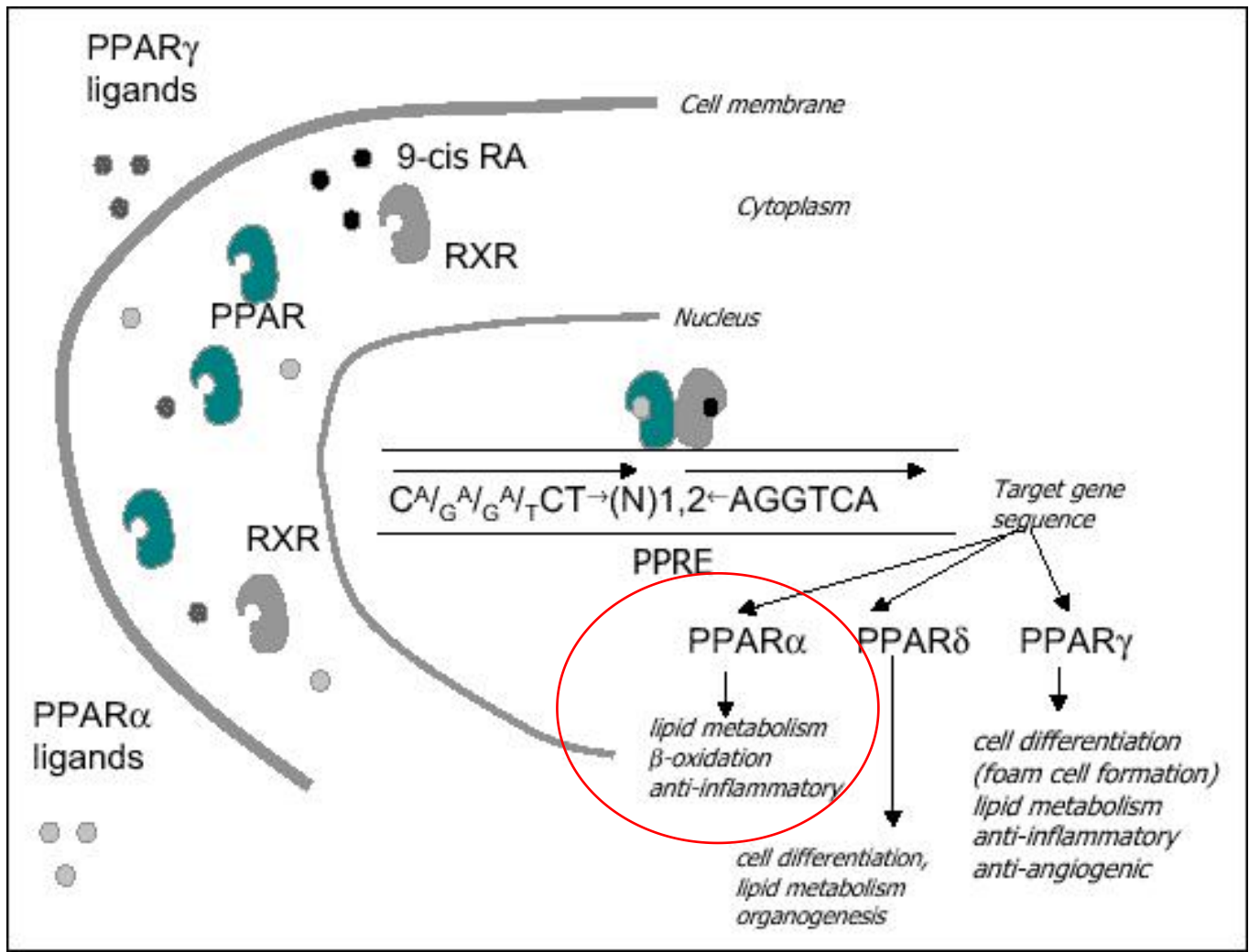


Fig. 1 Tissue-specific effects of fibroblast growth factor 21 (FGF21). In addition to adipose tissue and liver, FGF21 can target other organs, such as the pancreas where it protects against stress, acute inflammation, islet hyperplasia and general dysfunction [55, 112, 160–162], and heart [163–166], skeletal muscle [167, 168], kidney [169, 170], gut [171], brain [95, 147, 172, 173] and possibly bone [135], where it induces multiple biochemical signals and functional responses [60]. WAT, white adipose tissue; BAT, brown adipose tissue; FFA, free fatty acid.

Last quarter report review

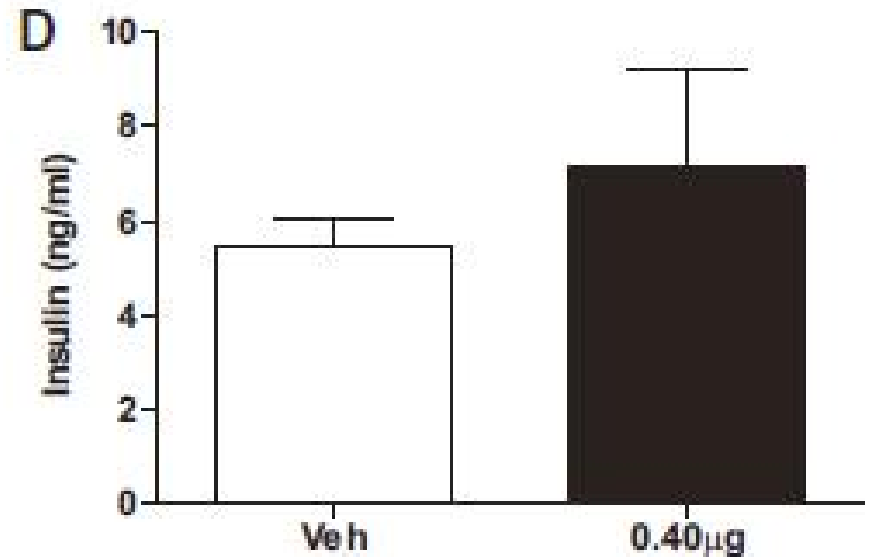
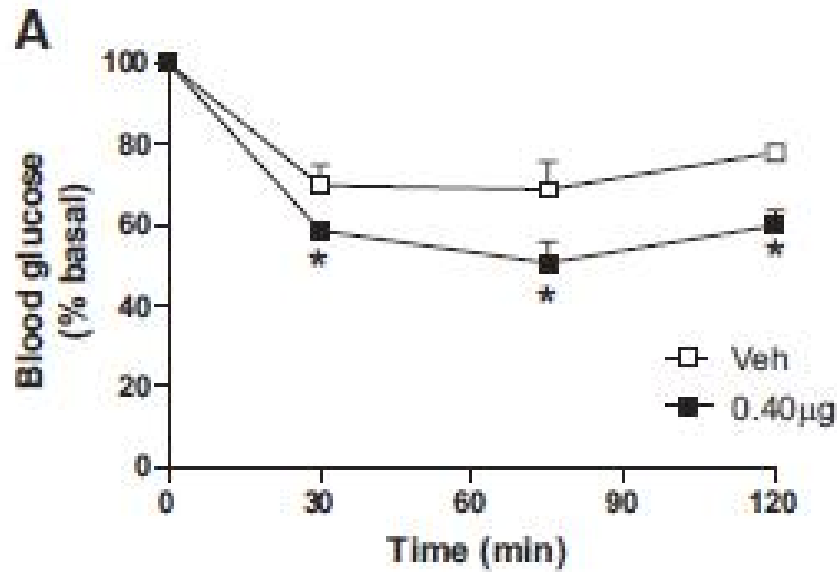
- A therapeutic dose of FGF21 **decreased blood glucose** in diabetic animals without causing hypoglycemia (4).
- FGF21 has also been shown to act as **a key downstream effector of PPAR α** , mediating several metabolic adaptation responses to starvation, including hepatic fatty acid oxidation, ketogenesis, and growth hormone resistance (1,2,7).



- In addition, FGF21 is implicated in **hepatic gluconeogenesis**, although it remains controversial whether hepatocytes are a direct action site of FGF21 (8,9)

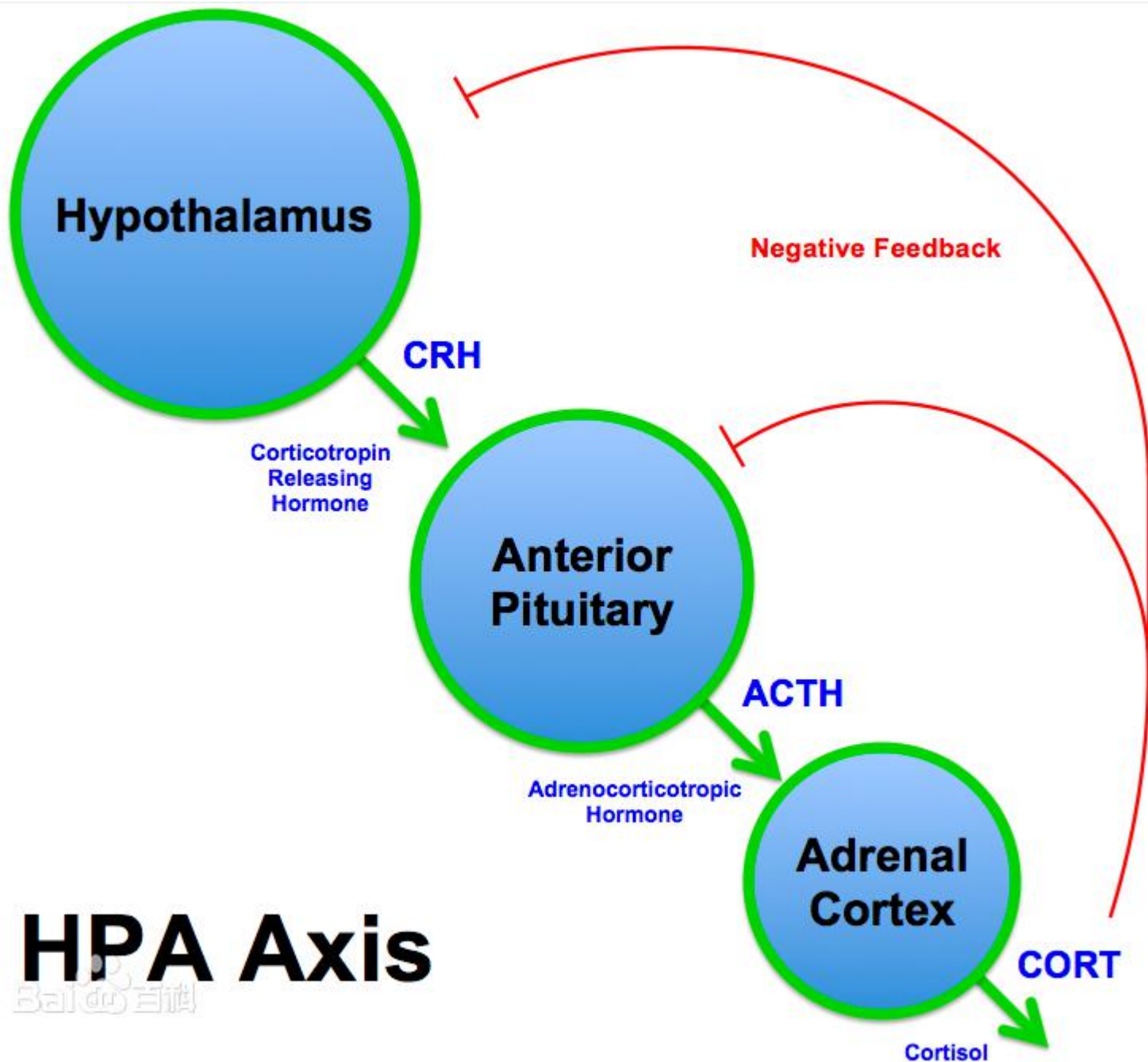
FGF-21 action in brain

Continuous intracerebroventricular injection of FGF-21

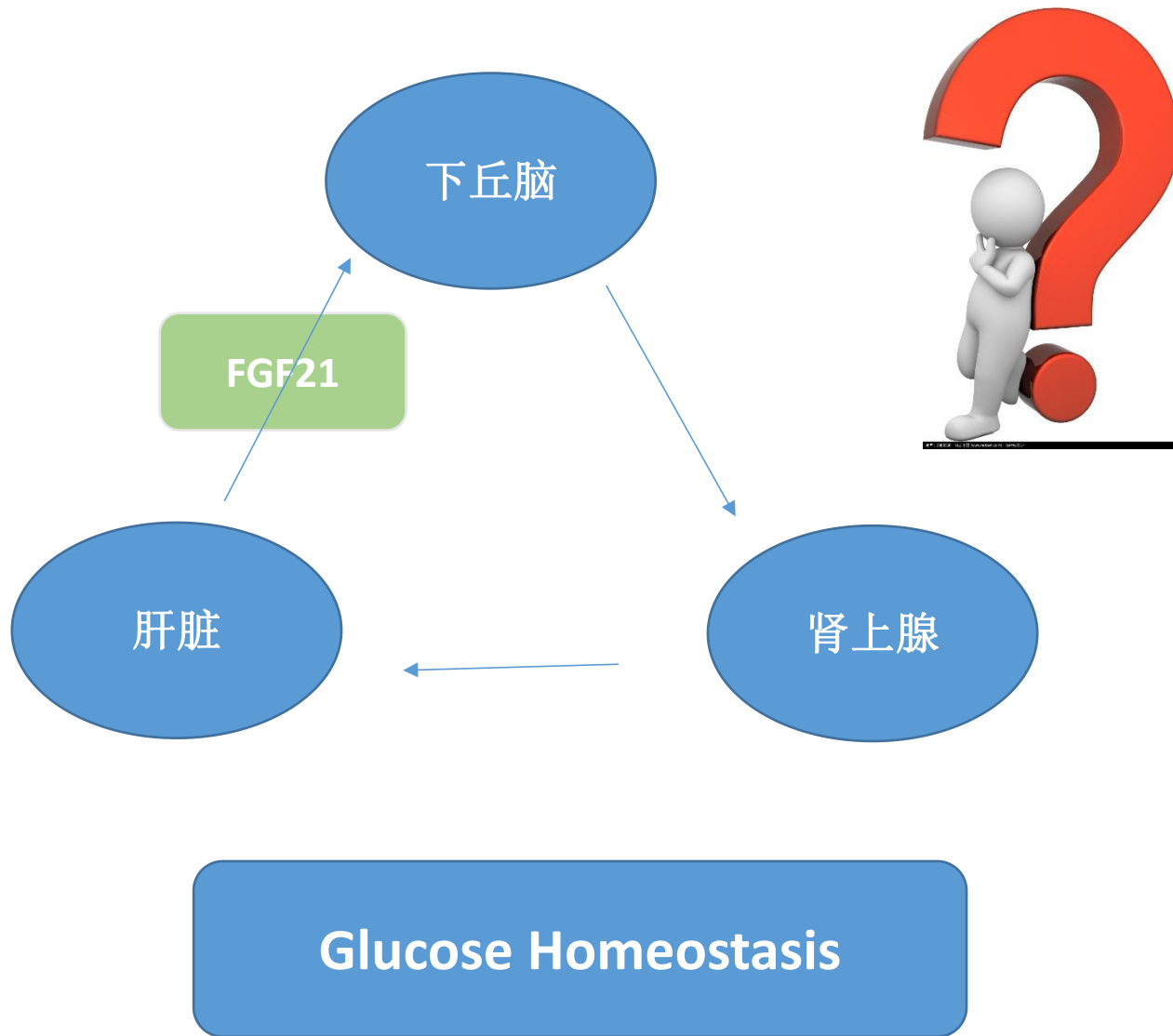


FGF21 action on the CNS

- FGF21 has been shown to act on the central nervous system to **increase systemic glucocorticoid levels**, suppress physical activity, and alter circadian behavior.
- FGF21 acts on the hypothalamus to **suppress the vasopressin-kisspeptin** signaling cascade, thereby mediating starvation induced infertility of female mice.
- However, the physiological roles of **FGF21 and its central actions in regulating glucose metabolism** during adaptive starvation responses remain unknown.



HPA Axis





PPAR α knockout (KO) mice in C57BL/6N

FGFR1



FGF21 KO mice in C57BL/6J

CRH antagonist

endotoxin-free

recombinant mouse FGF21

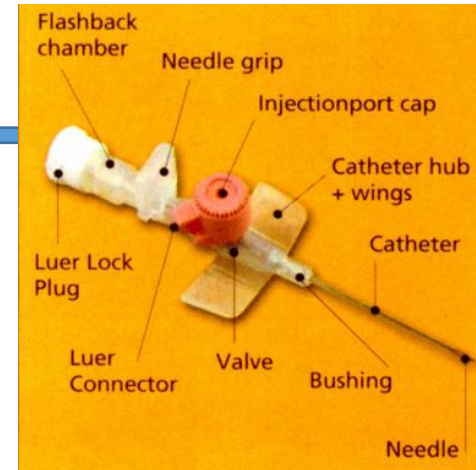


WT

Bilateral or sham adrenalectomy

was conducted under isoflurane anesthesia 1 week

before various fasting experiments.

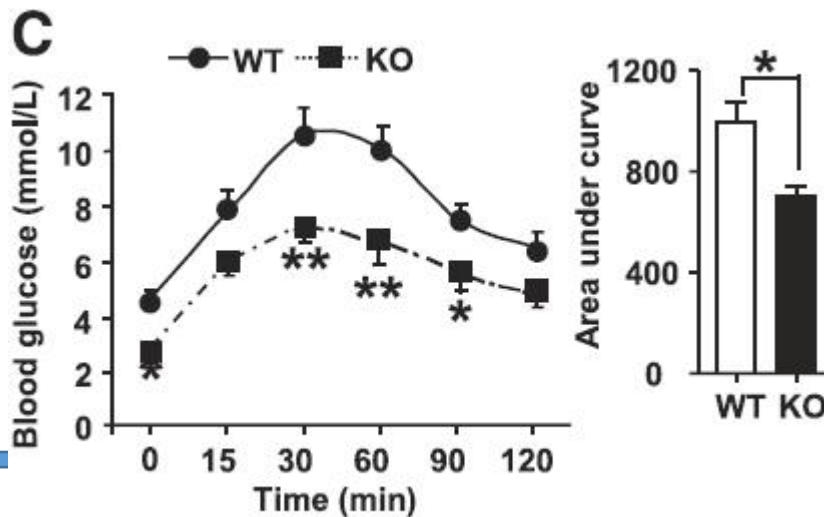
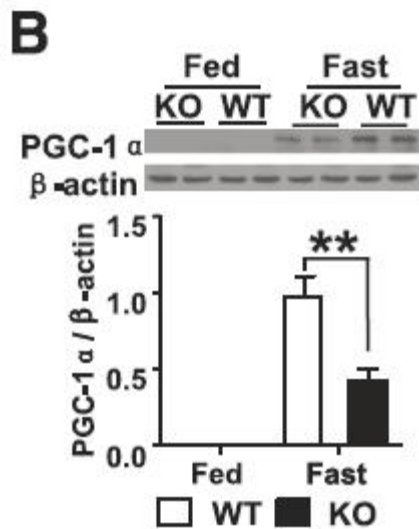
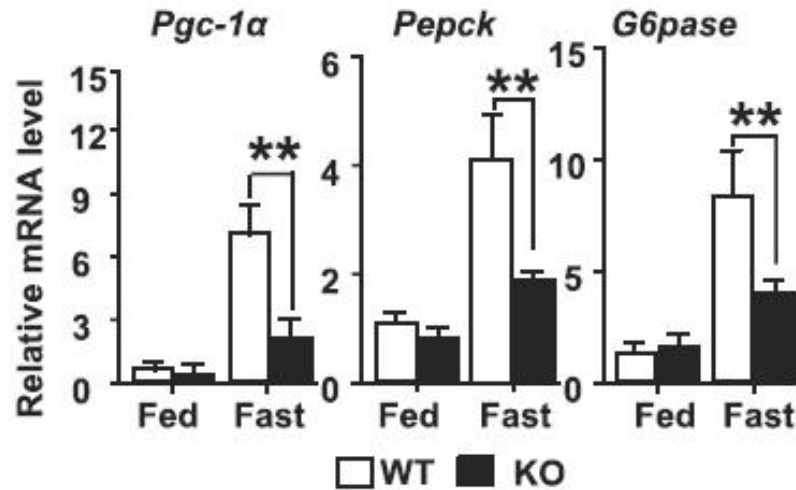
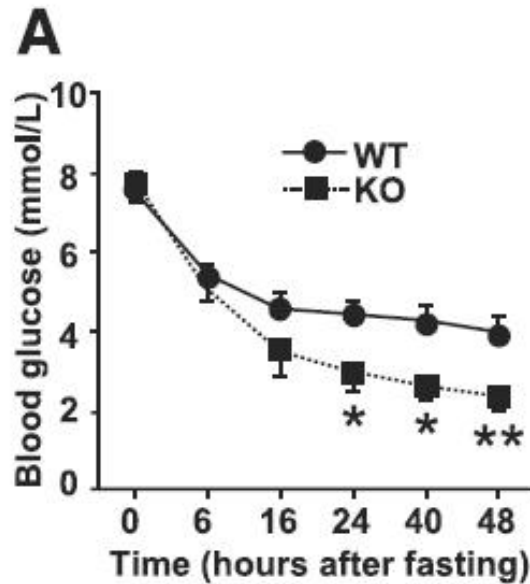


intra-PVN injection

central administration

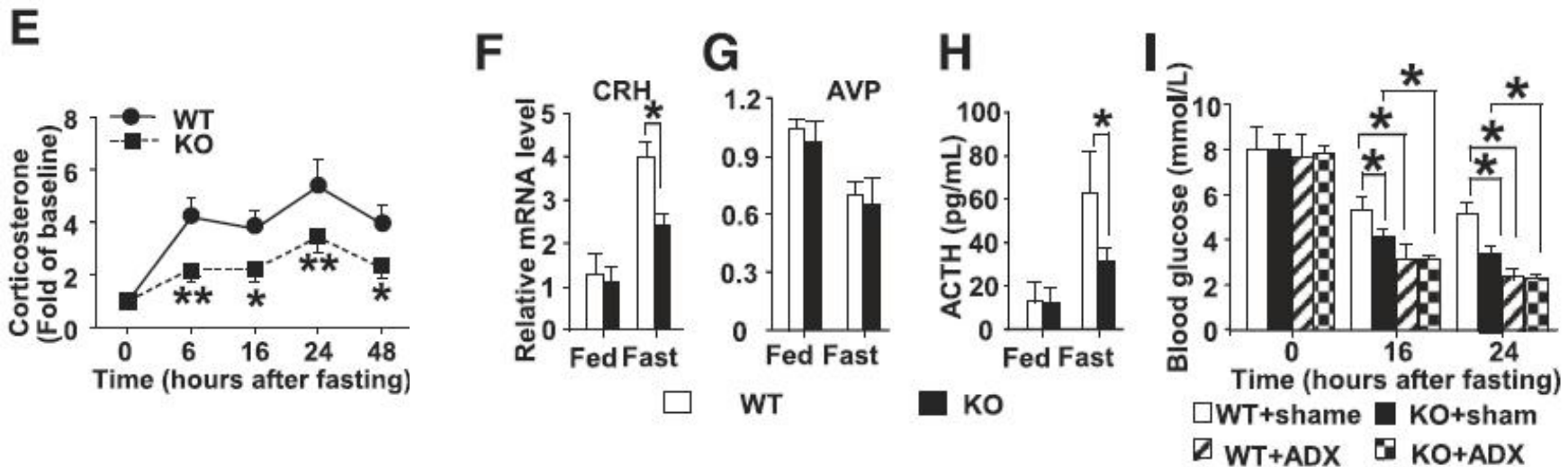
- Immunoassays:
- Serum levels of **insulin** and **FGF21**
- Serum levels of **corticosterone** (Enzo Life Sciences) and **glucagon** (Millipore) and plasma levels of **adrenocorticotrophic hormone** (ACTH; MD Bioproducts) and CRH (Phoenix Pharmaceuticals)
- For analysis of **adrenaline** and **noradrenaline** in the liver, frozen tissue was extracted with 0.1 N HCl and analyses performed according to the supplier's instructions

FGF21 KO Mice Exhibit Hypoglycemia During Prolonged Fasting



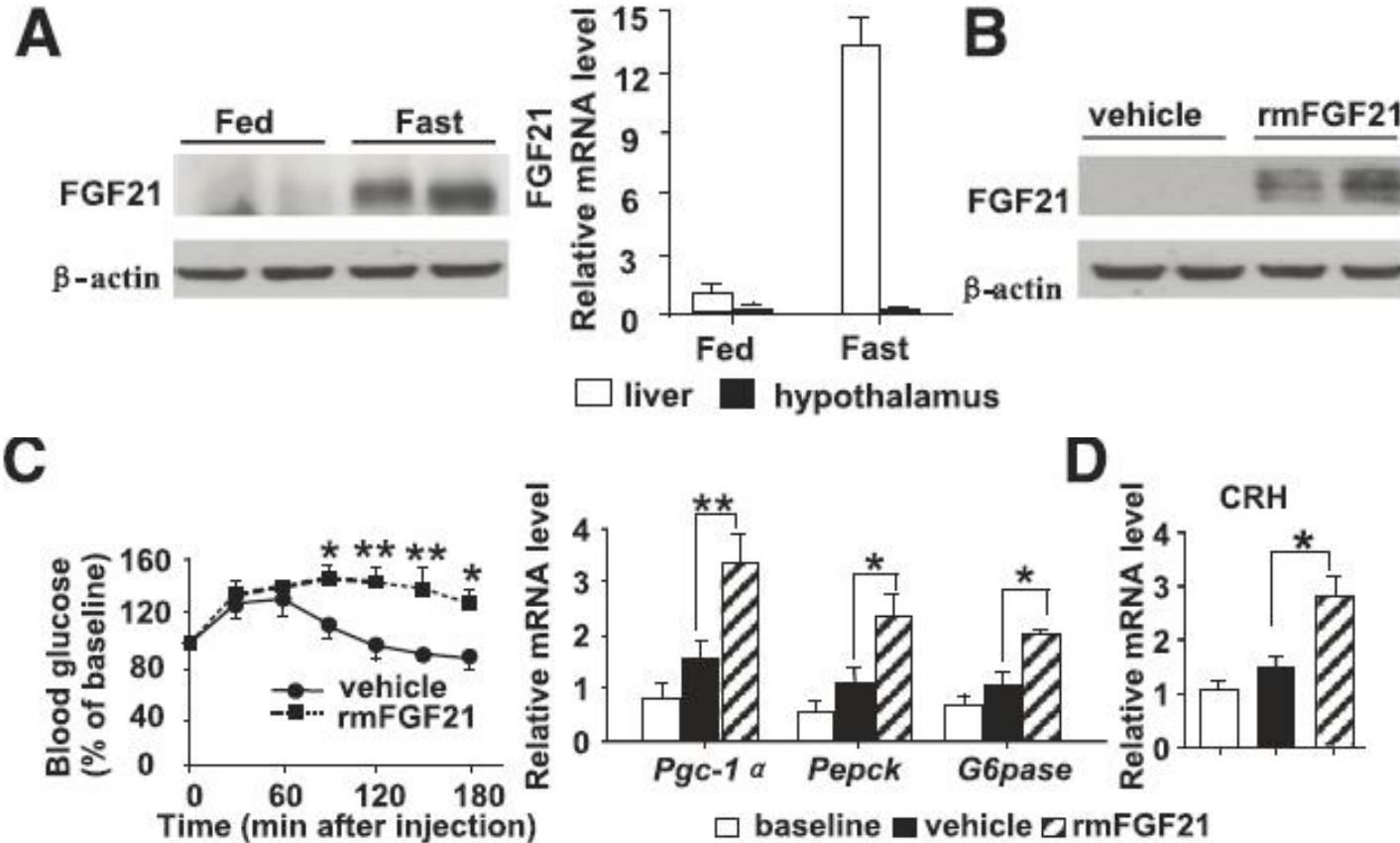
Pyruvate tolerance test was performed in 24 h-fasted FGF21 KO mice

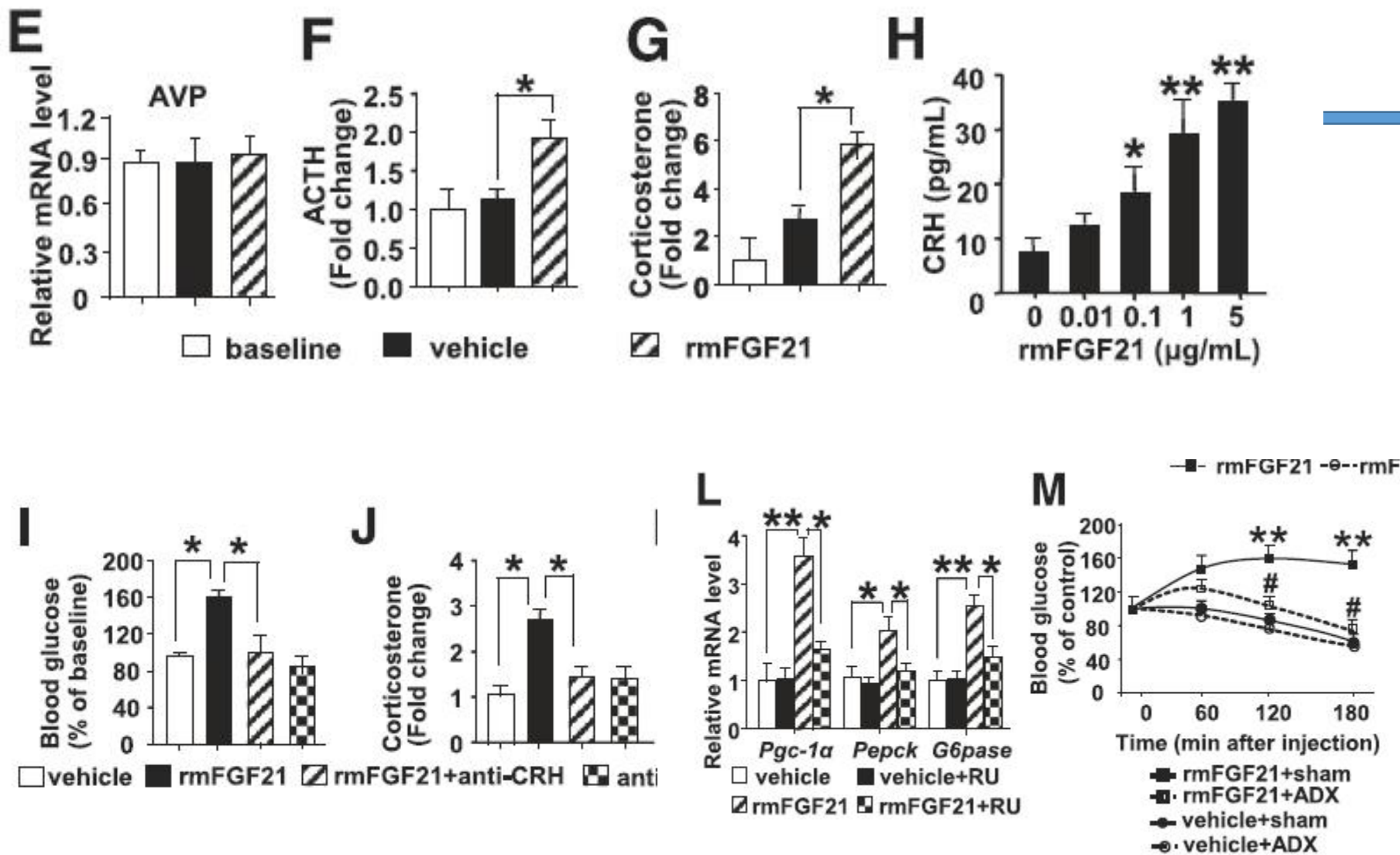
FGF21 Deficiency Impairs Fasting-Induced Activation of the Hypothalamic-Pituitary-Adrenal Axis and Release of Corticosterone in Mice



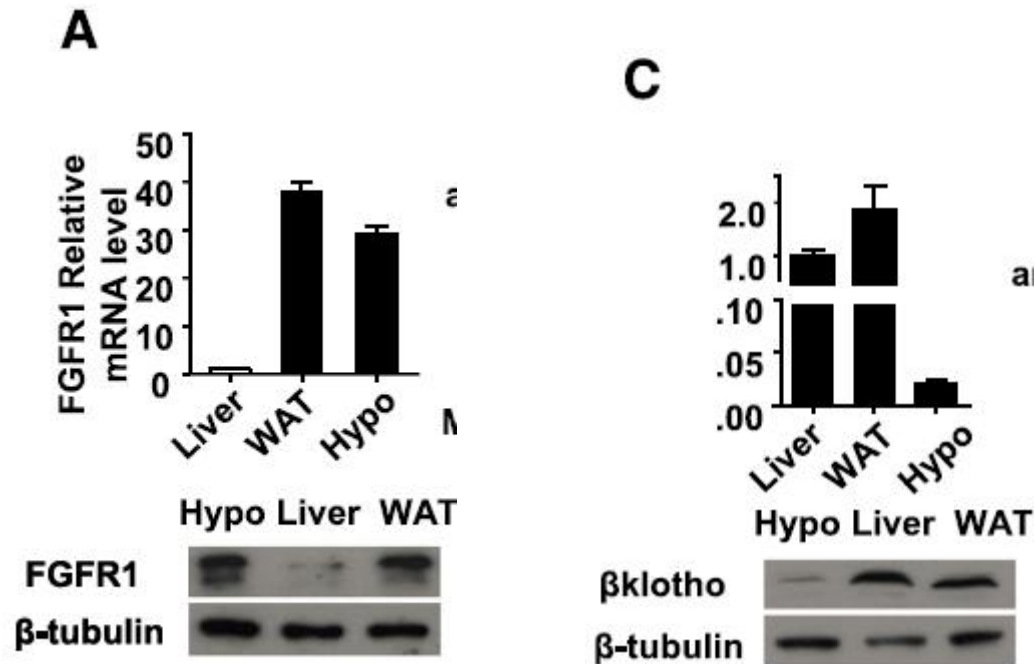
adrenalectomy 肾上腺切除

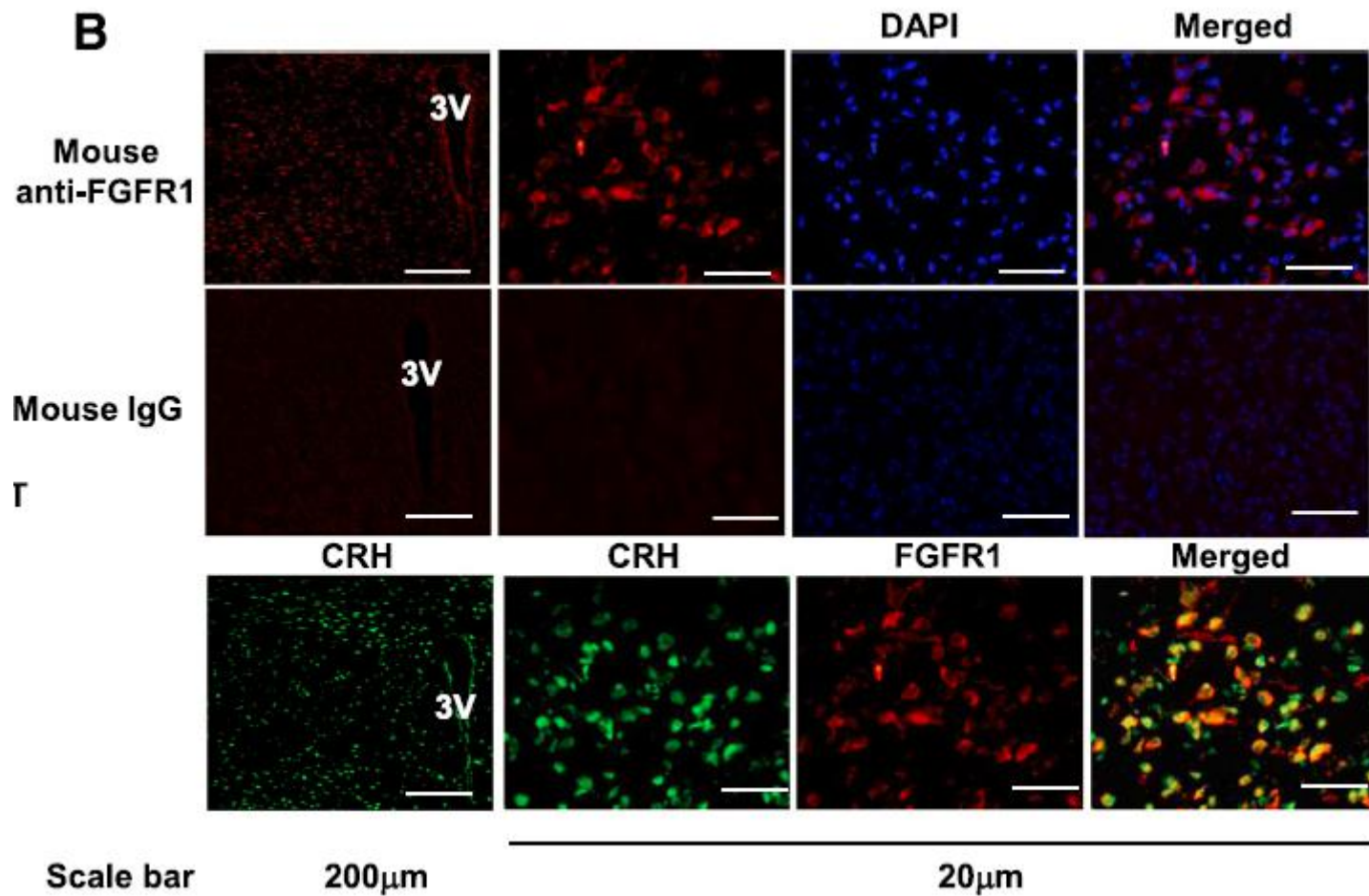
FGF21 Acts in the Brain to Induce Corticosterone Production and Hepatic Gluconeogenesis

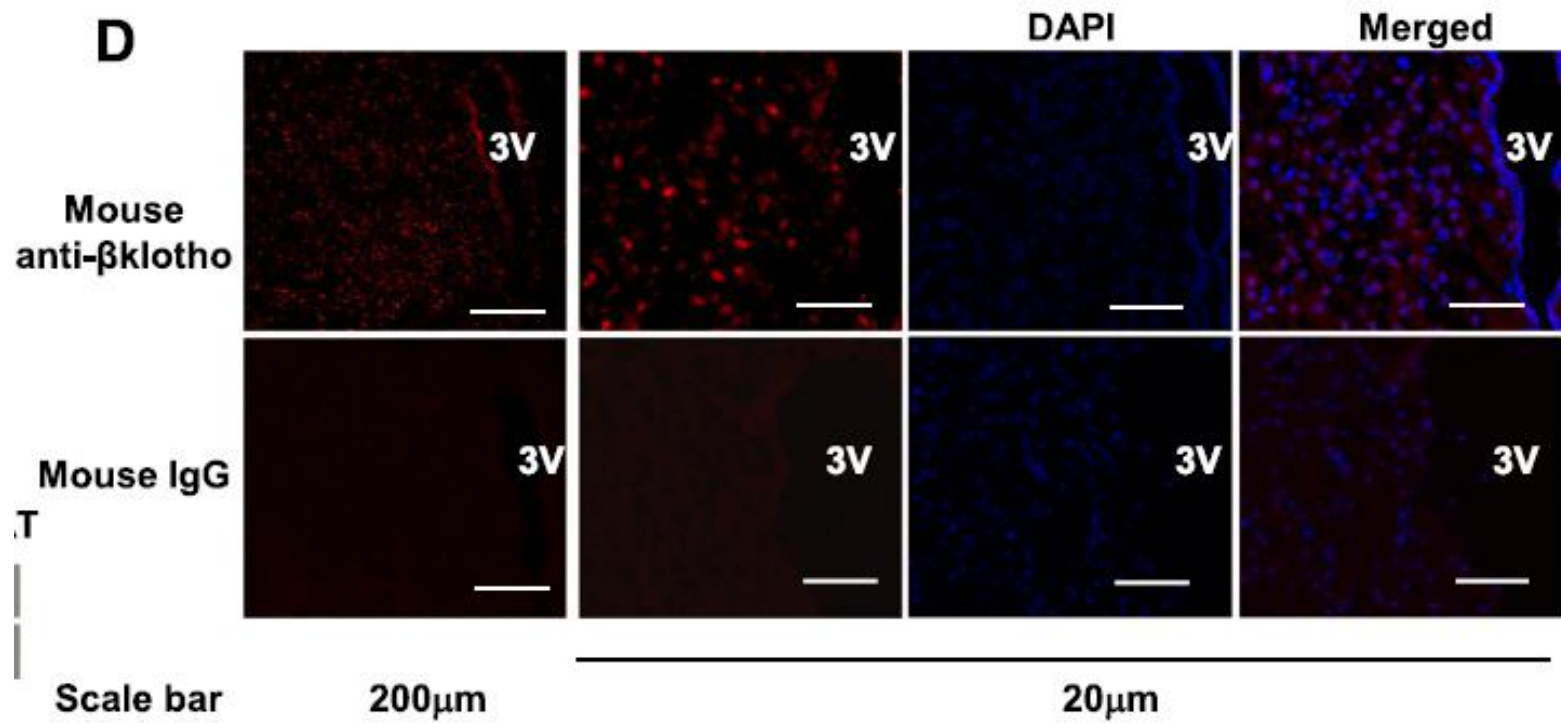




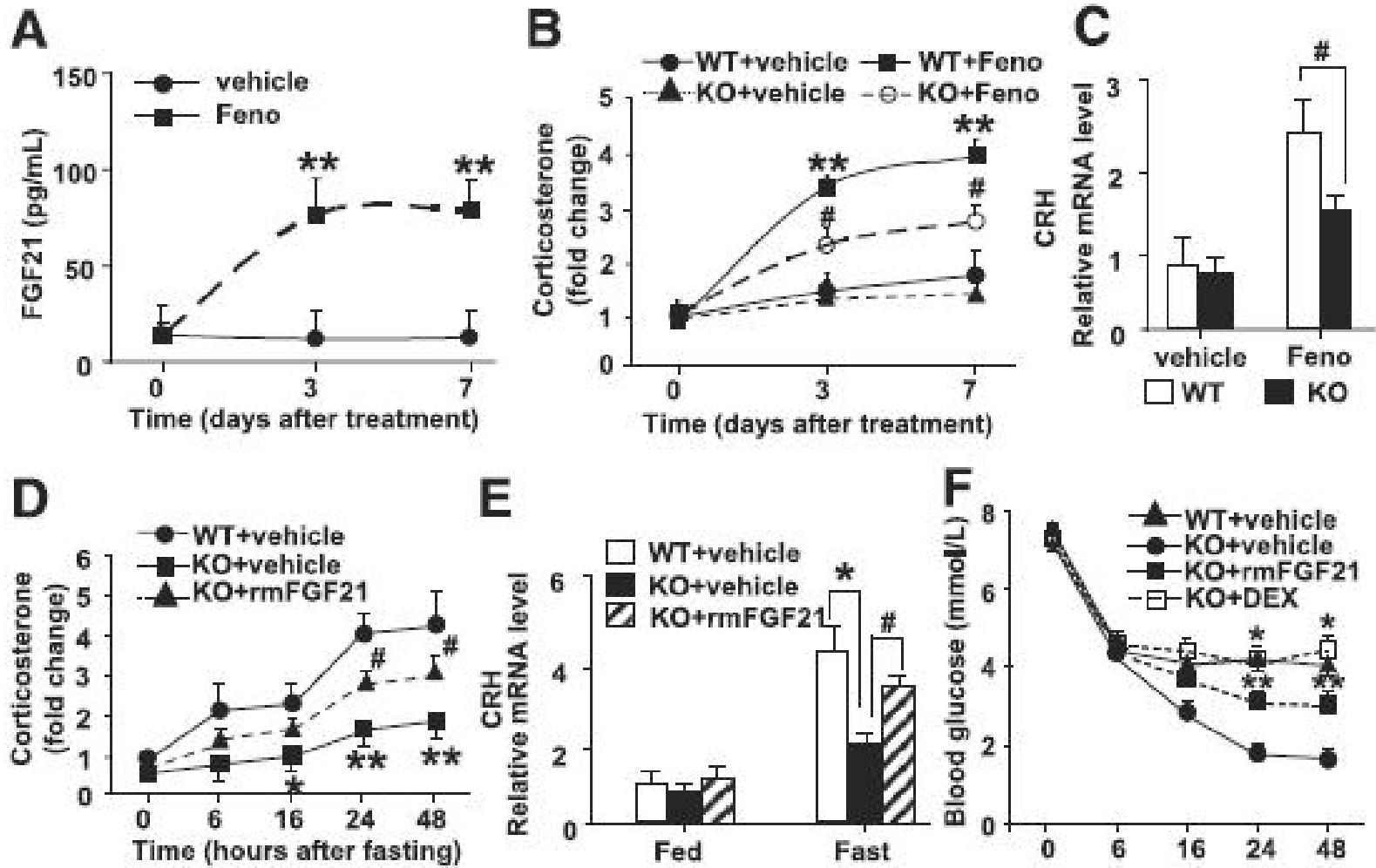
Central Effects of FGF21 on Activation of the HPA Axis and Hepatic Gluconeogenesis Are Mediated by Hypothalamic FGFR1

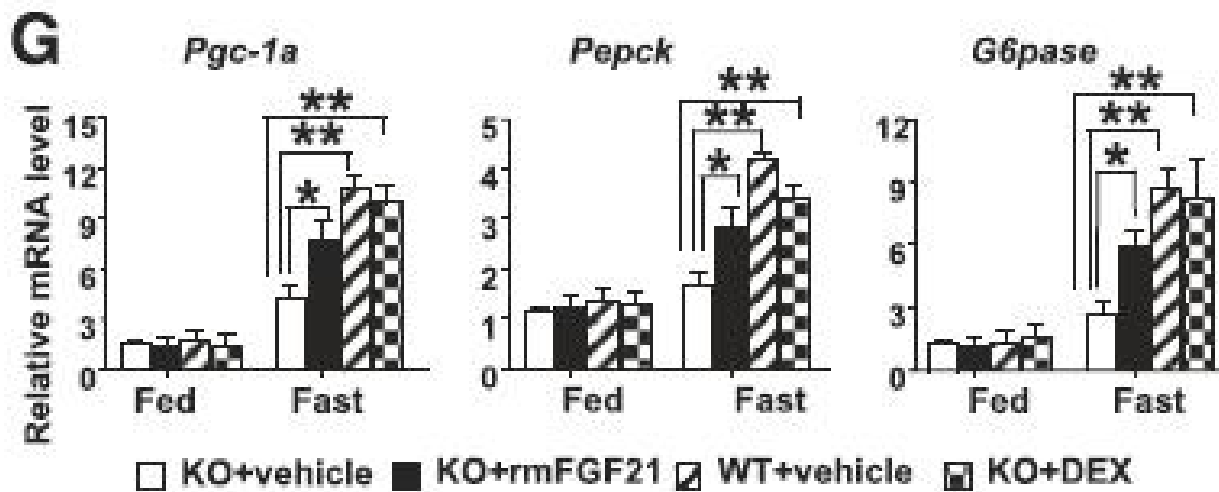


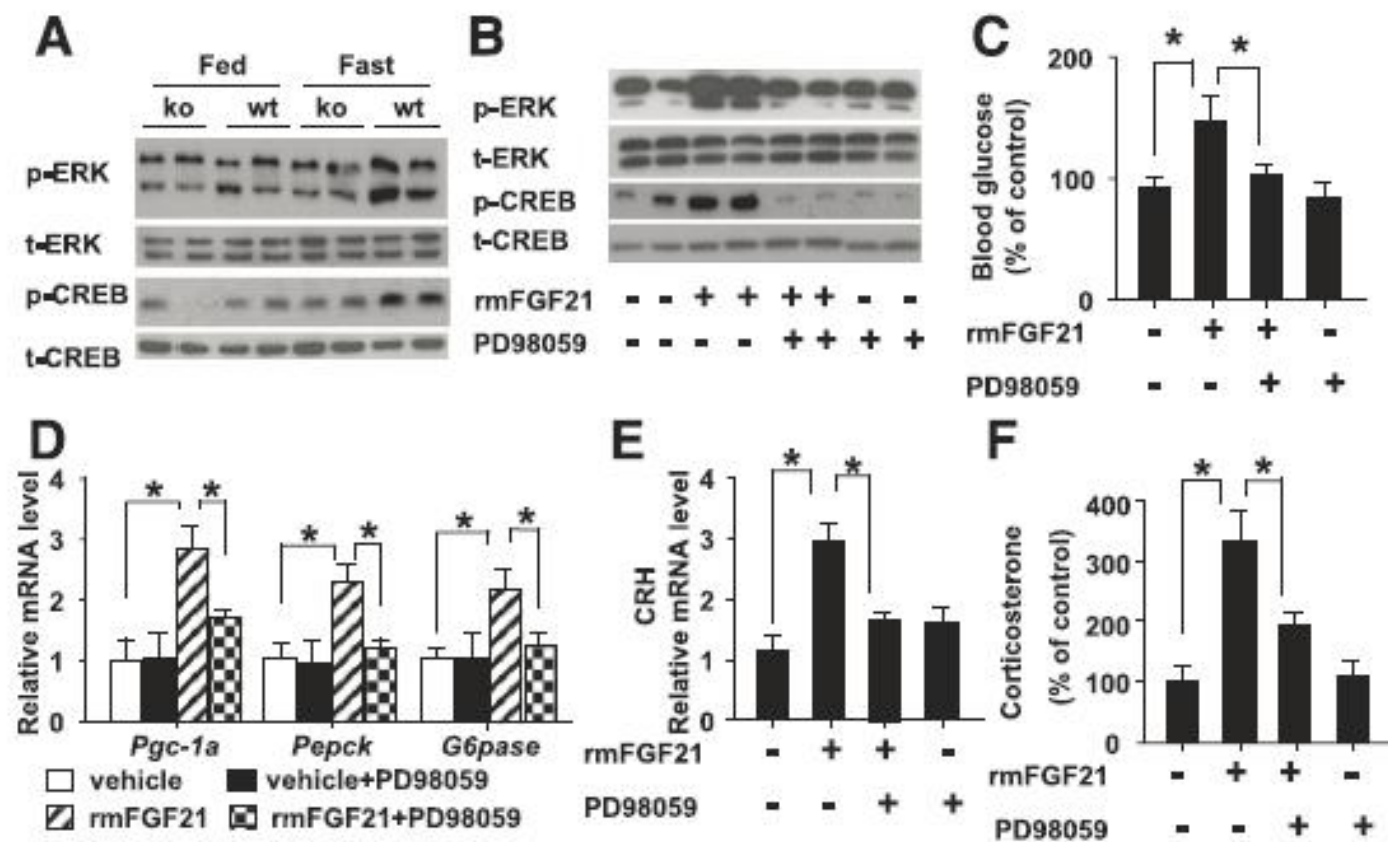




FGF21 Mediates PPAR α -Induced Corticosterone Production and Hepatic Gluconeogenesis in Mice via Central Nervous System







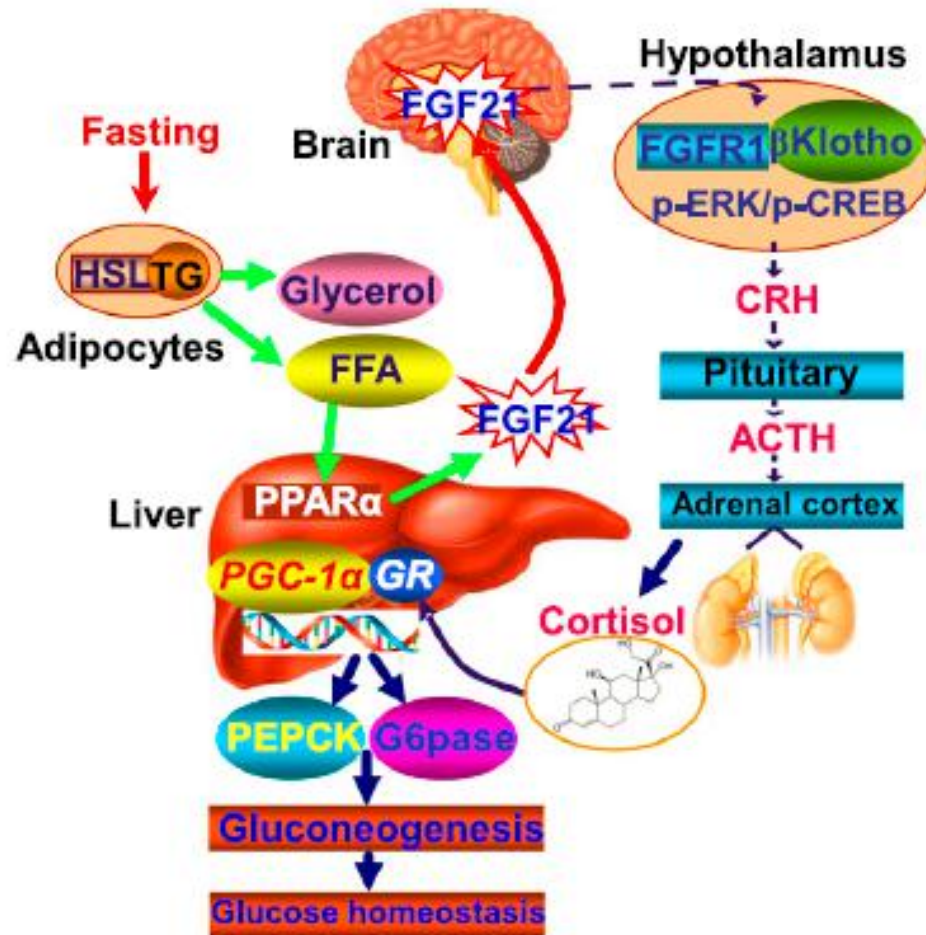


Figure 8—A working model by which FGF21 maintains glucose homeostasis during fasting via mediating the cross talk between brain and liver. FFA, free fatty acids; HSL, hormone-sensitive lipase; TG, triglycerides.

THANKS!