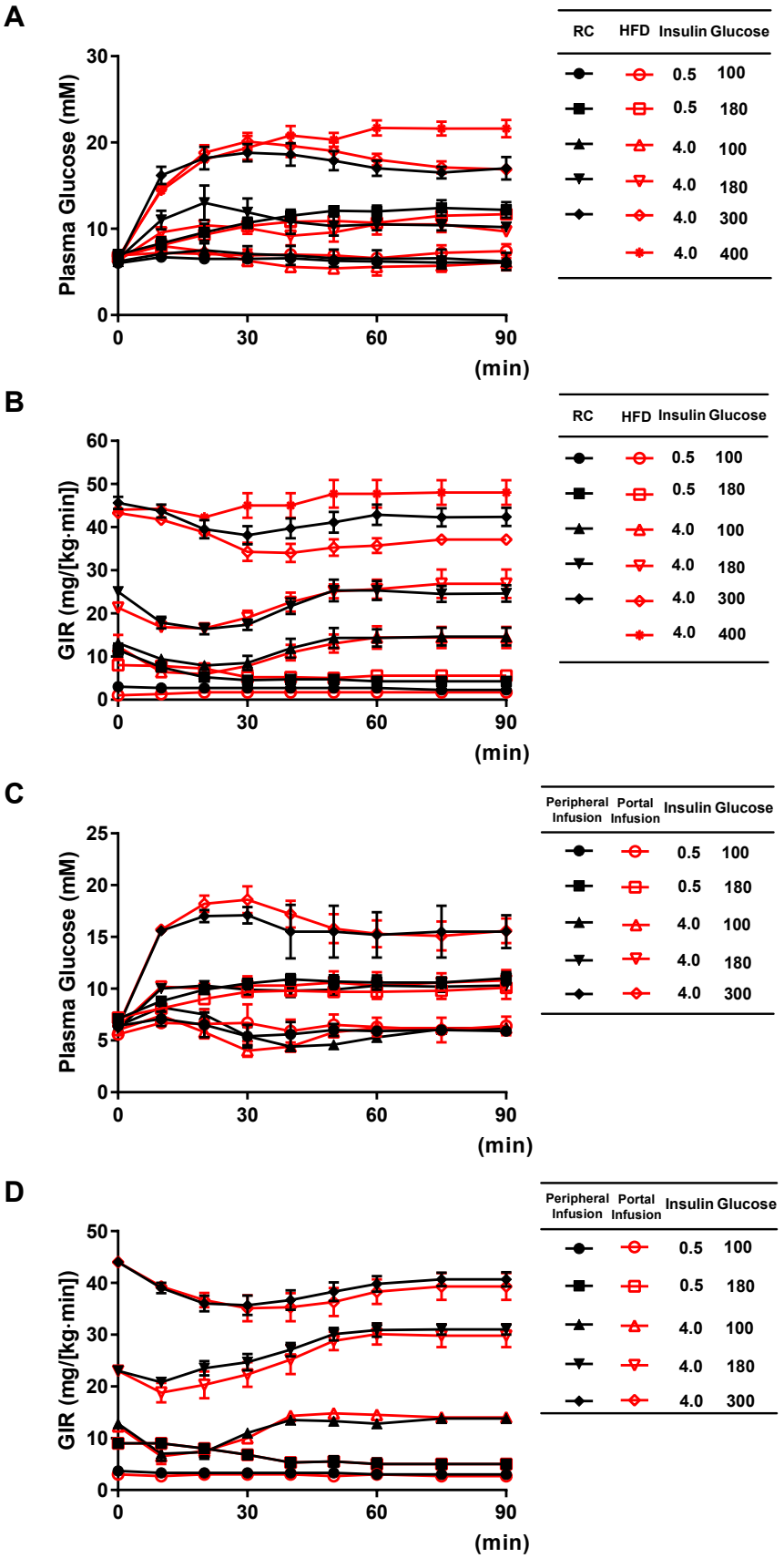


Fig.S1. Somatostatin pancreatic clamps in control and HFD groups

Rats were fed either regular chow (black bars) or 3-day HFD (red bars) and subjected to somatostatin pancreatic clamps at the insulin infusion rates and target plasma glucose levels listed.

(A) Plasma glucose concentrations during clamp studies. (B) Glucose infusion rates during clamp studies.

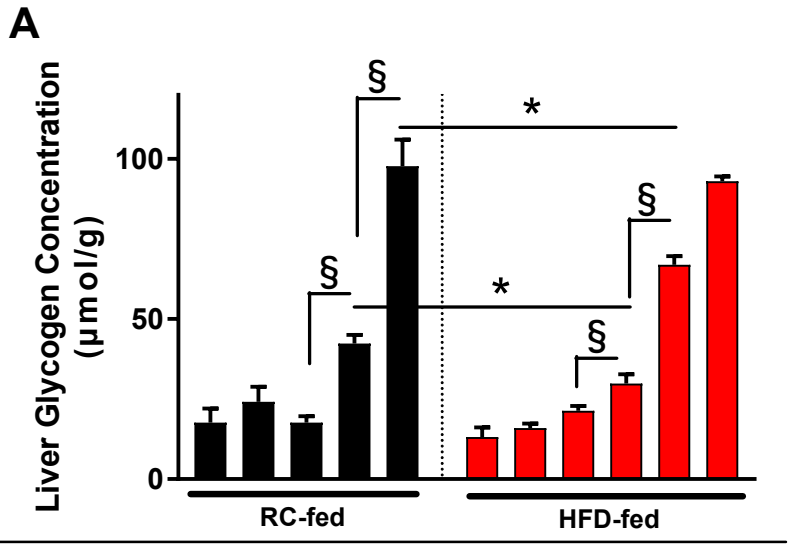
Somatostatin pancreatic clamps in peripheral and portal glucose infusion models

Rats were fed regular chow and subjected to somatostatin pancreatic clamps at the insulin infusion rates listed. Controls (black bars) received glucose infusions targeting the plasma glucose concentrations listed, and the portal delivery group (red bars) received a matched glucose infusion rate.

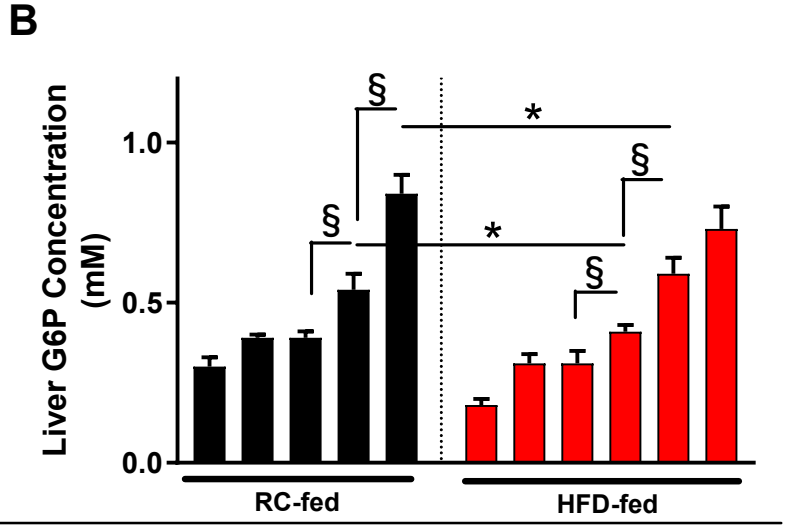
(C) Plasma glucose concentrations during the clamp, (D) Glucose infusion rates during the clamp.

Data are the mean±SEM of n= 3 to 18 per group.

www.pnas.org/cgi/doi/10.1073/pnas.1921694117



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300	400



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300	400

Fig.S2. Hepatic glycogen concentration and hepatic G6P concentration in control and HFD groups
Rats were fed either regular chow (black bars) or 3-day HFD (red bars) and subjected to somatostatin pancreatic clamps at the insulin infusion rates and target plasma glucose levels listed below the x-axis. (A) Total hepatic glycogen concentration, and (B) hepatic G6P concentration in control and HFD groups following the clamp study.
Data are the mean±SEM of n= 3 to 13 per group. Statistical analysis reported for comparisons of hepatic glycogen concentration and hepatic G6P concentration. Within a diet-group (RC or HFD fed), all groups were compared with all other groups, with statistics by ANOVA with post hoc testing. Between diet groups, rats subject to identical infusion strategies were compared, with statistics by unpaired Student's t test. *p<0.05 by unpaired Student's t test and §p<0.05 by ANOVA followed by post hoc test.

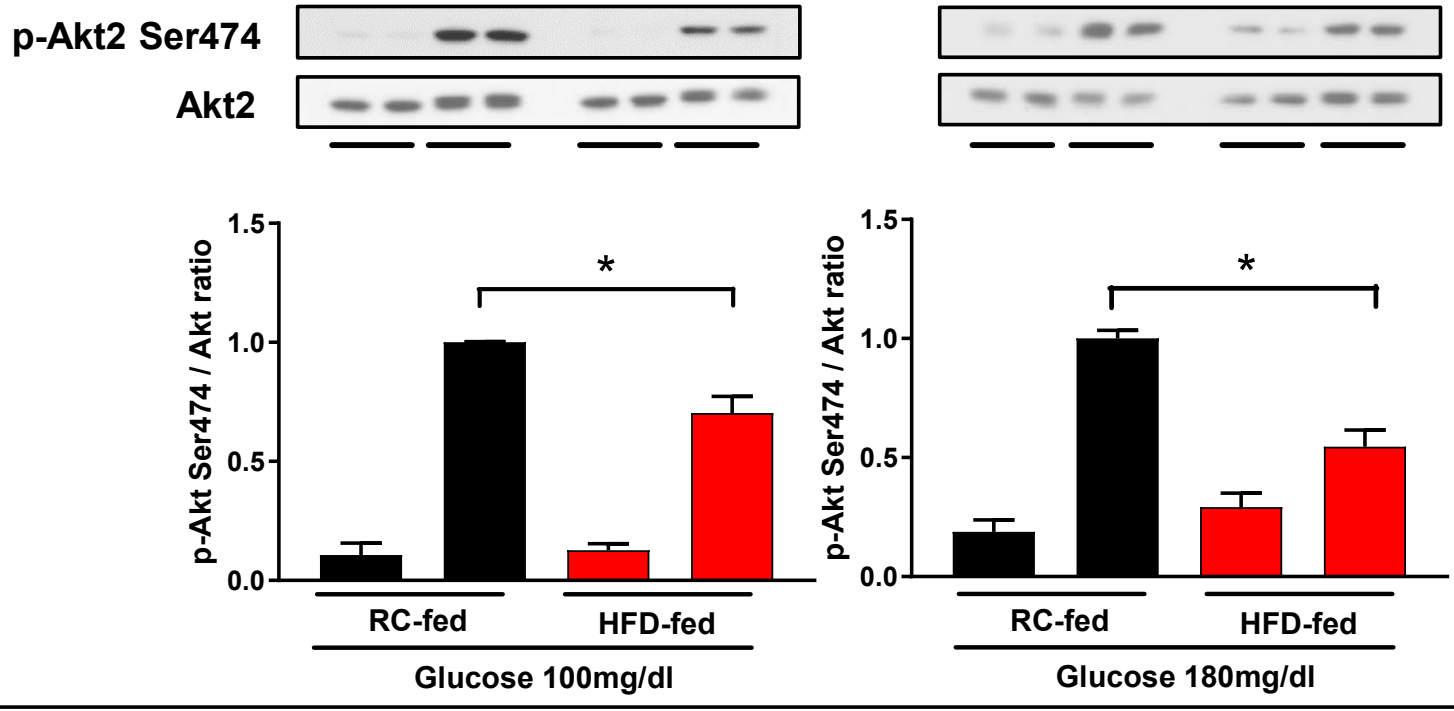
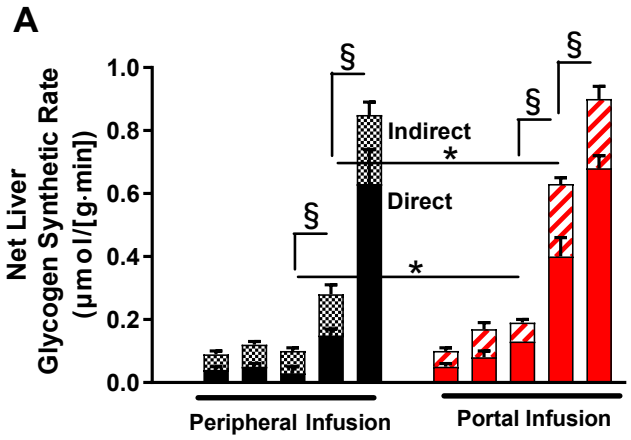
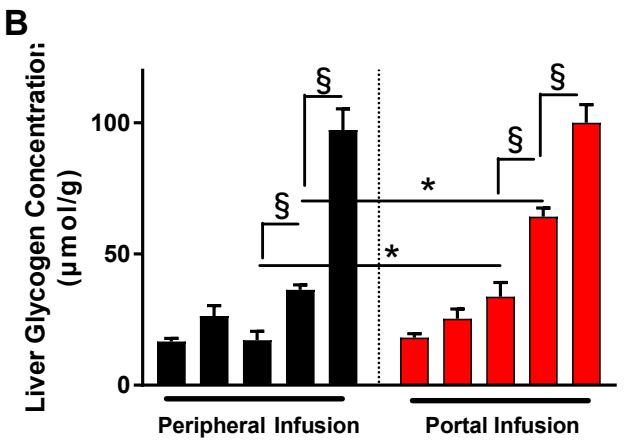


Fig.S3. Intrahepatic insulin resistance in 3 day HFD-fed rats

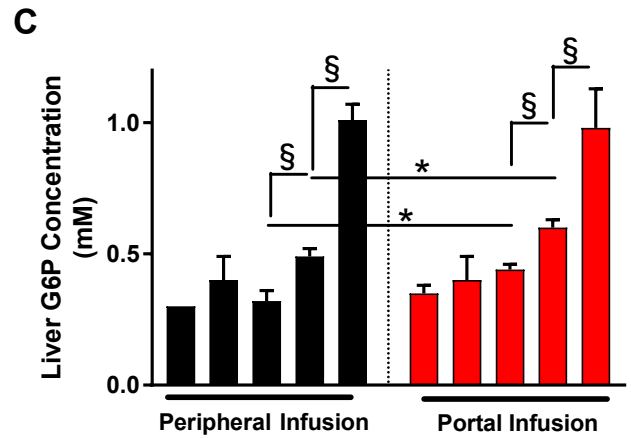
Rats were fed either regular chow (black bars) or 3-day HFD (red bars) and subjected to somatostatin pancreatic clamps at the insulin infusion rates and target plasma glucose levels listed below the x-axis. Liver AKT2 phosphorylation in post-clamp liver. Data are the mean±SEM of n= 4 per group. *p<0.05 by unpaired Student's t test.



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300

Fig.S4. Hepatic glycogen synthesis during peripheral or portal dextrose infusion

Rats were fed regular chow and subjected to somatostatin pancreatic clamps at the insulin infusion rates listed. Peripherally infused rats (black bars) received dextrose infusions targeting the plasma glucose concentrations listed below the x-axis., while the portal delivery group (red bars) received dextrose infusions at matched glucose infusion rate to the peripherally infused rats.

(A) Net hepatic glycogen synthetic rates are represented in the bar graph, the solid part of the bar represents direct pathway synthesis and the patterned part of the bar represents indirect pathway synthesis,

(B) Total hepatic glycogen concentration, and (C) Hepatic G6P concentration following the clamp study.

Data are the mean±SEM of n= 3 to 18 per group. Statistical analysis reported for comparisons of net glycogen synthetic rates, hepatic glycogen concentration and hepatic G6P concentration. Within a delivery-group (peripheral or portal delivery), all groups were compared with all other groups, with statistics by ANOVA with post hoc testing. Between delivery-groups, rats subject to identical infusion strategies were compared, with statistics by unpaired Student's t test. *p<0.05 by unpaired Student's t test and §p<0.05 by ANOVA followed by post hoc test.

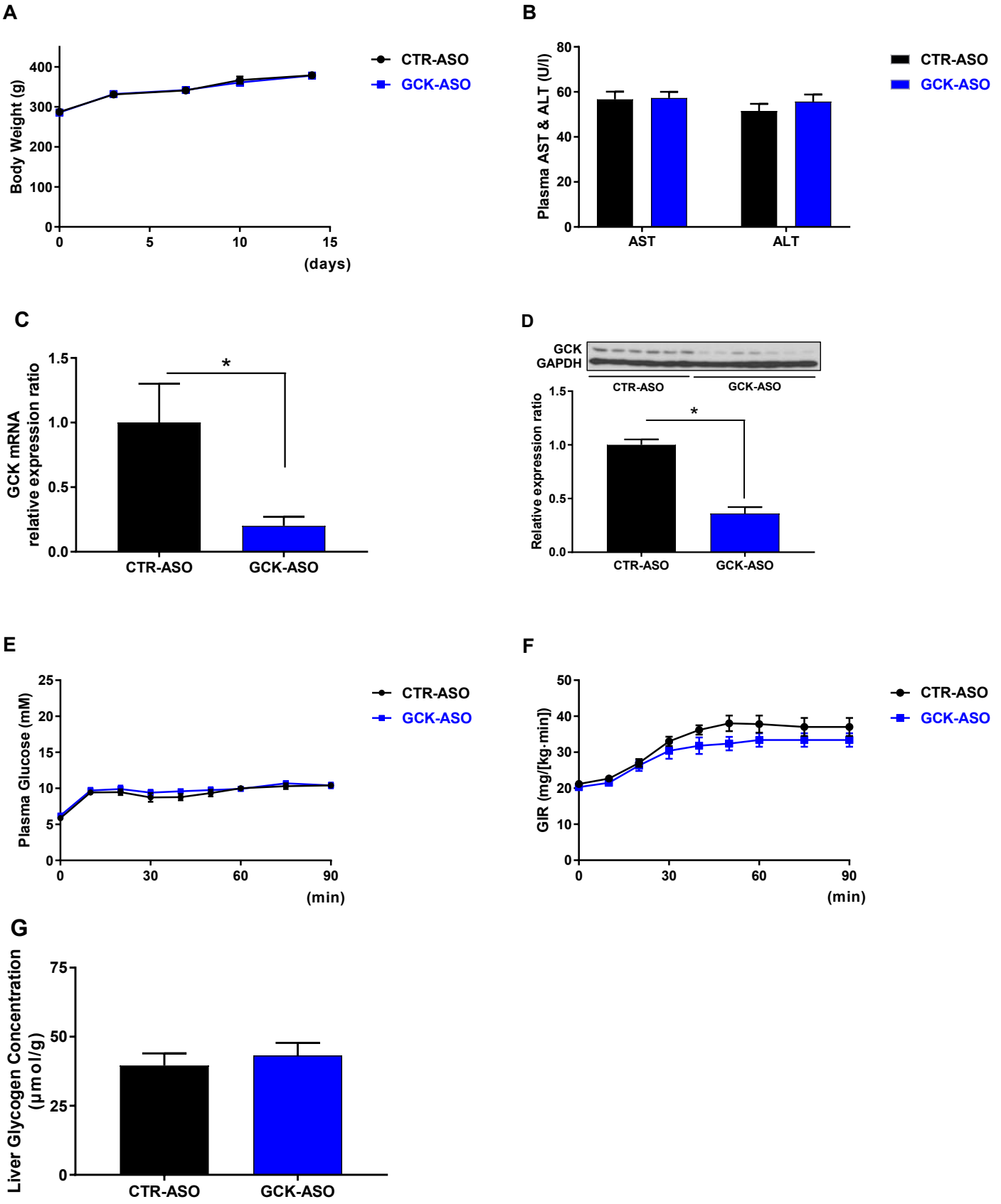


Fig.S5. Efficacy and nontoxicity of GCK ASO treatment

Rats were treated with GCK (blue bars) or control (black bars) ASO for 2 weeks and hyperinsulinemic-hyperglycemic clamp studies were performed.

(A) Body weight during ASO treatment.

(B) Plasma AST and ALT activity prior to clamp studies.

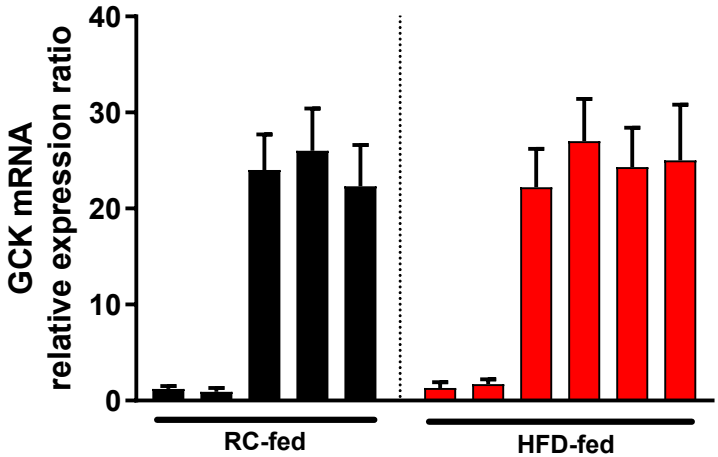
(C) GCK mRNA expression measured by qPCR.

(D) GCK protein expression measured by immunoblotting of liver lysate, normalized to GAPDH.

(E) Plasma glucose concentrations and (F) glucose infusion rates during the clamp.

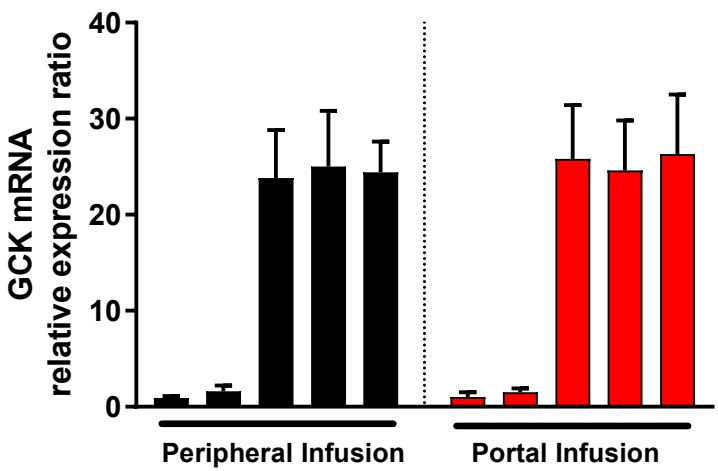
(G) Total hepatic glycogen concentration. Data are the mean±SEM of n= 6 to 9 per group. *p<0.05 by unpaired Student's t test.

A



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300	400

B



Insulin Infusion Rate (mU/[kg·min])	0.5	0.5	4.0	4.0	4.0	0.5	0.5	4.0	4.0	4.0
Target Glucose Concentration (mg/dl)	100	180	100	180	300	100	180	100	180	300

Fig.S6. Mechanism of activation of GCK as rate-controlling step
(A-B) qPCR measurement of GCK mRNA in (A) control (black bars) and HFD groups (red bars), and (B) control (black bars) and portal delivery groups (red bars).
Data are the mean±SEM of n= 3 to 4 per group.