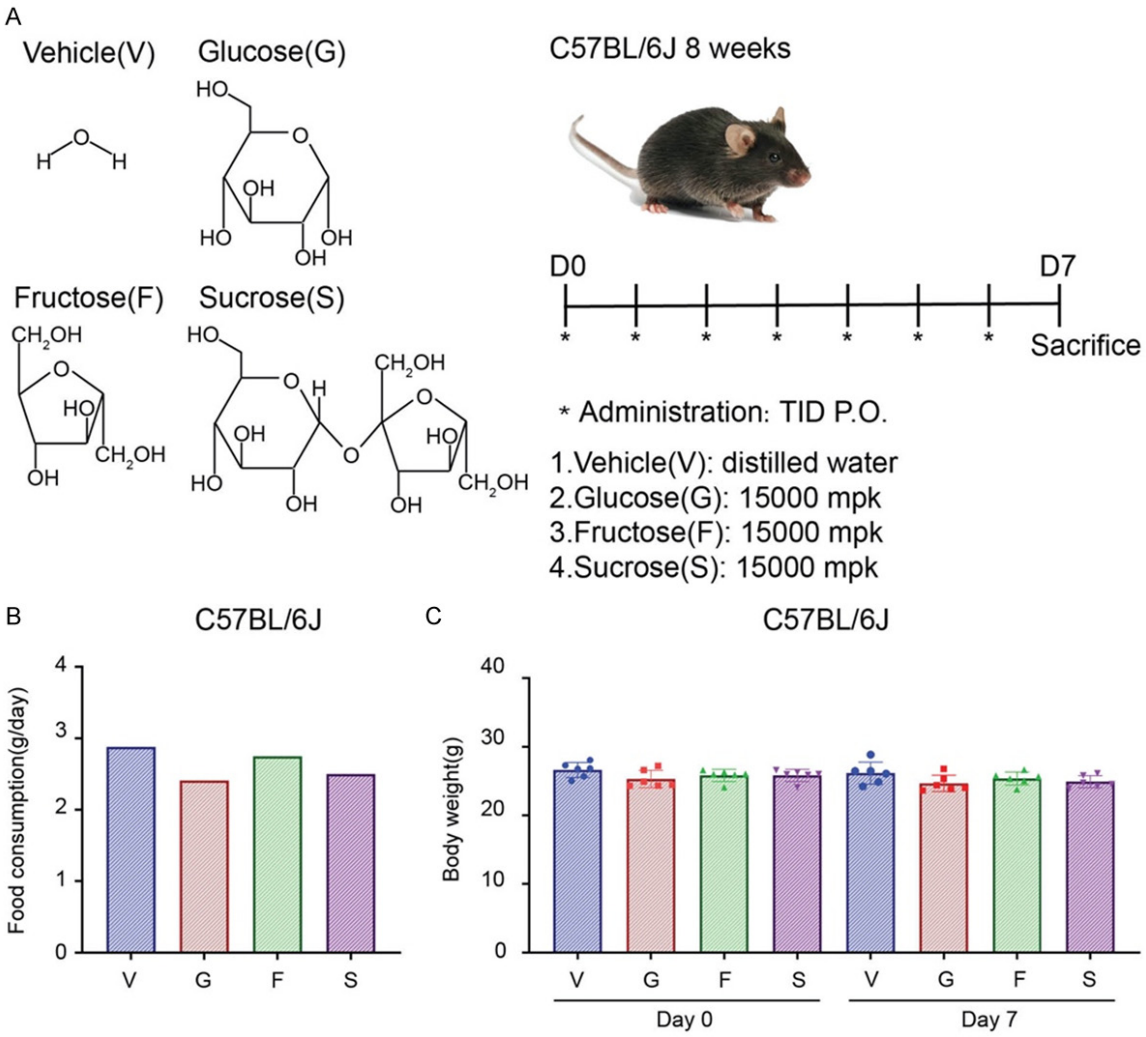
Supplementary Table 1. Macro-nutrition (calories, %) provided by a chow diet and a high sugar diet

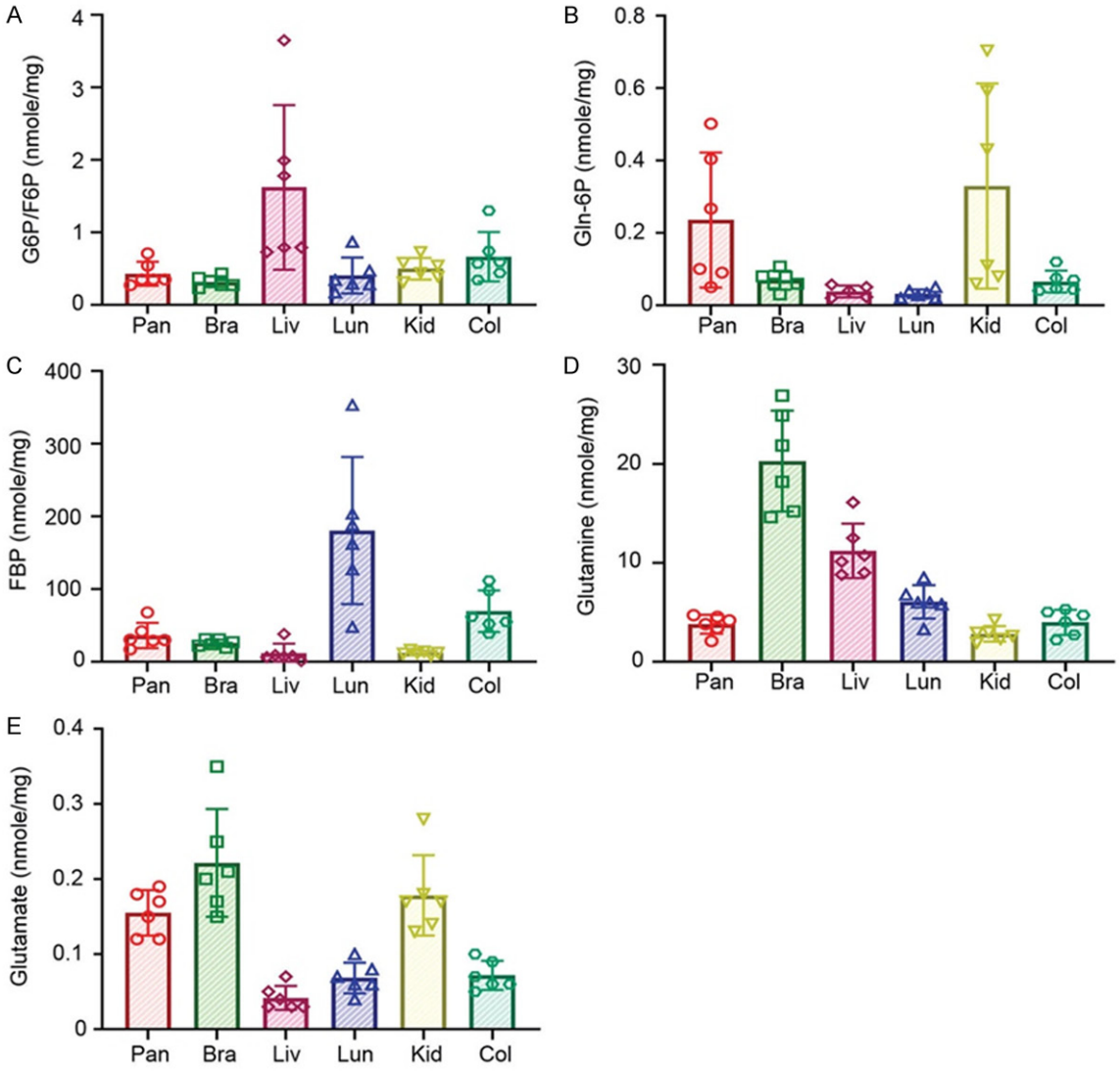
Ingredients	Chow diet	High sugar diet
Protein	28.5	26.45
Fat	13.42	12.49
Carbohydrate	58.08	61.06
Of which starch	18.53	2.7
Of which glucose	0.13	9.09
Of which fructose	0.17	9.09
Of which sucrose	2.15	20.24

Supplementary Table 2. Antibodies in this study

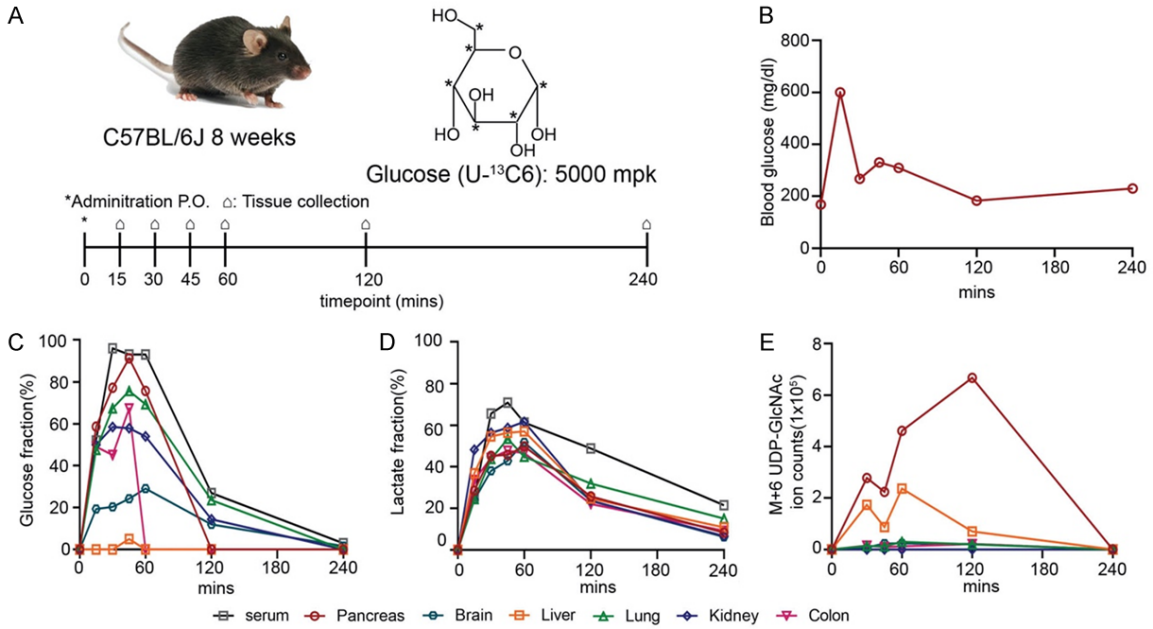
Antibodies	Brand	Cat. No.	Application & dilution
γH2AX	Merck Millipore	05-636	ICC-1:1000
γH2AX	Cell sig. tech.	#9718	IHC-1:100
110.6	Cell sig. tech.	#9875	IHC-1:1000
GFAT1	Genetex	GTX64638	WB-1:1000
GFAT2	Genetex	GTX66370	WB-1:1000
PFKL	Genetex	GTX105697	WB-1:1000
PFKM	Genetex	GTX111597	WB-1:1000
PFKP	Genetex	GTX107857	WB-1:1000
OGT(DM-17)	Sigma	O-6264	WB-1:1000
OGA	Sigma	SAB4200311	WB-1:5000
p84	Genetex	GTX70220	WB-1:10000
RRM1	Genetex	GTX54666	WB-1:10000
RRM1	Santa Cruz	sc-11733	IP-1:500
RL2	Abcam	Ab2739	WB-1:1000, ICC-1:500
Ki67	Abcam	Ab15580	IHC-1:1000
Donkey anti-Mouse IgG Alexa Fluor 488 antibody	Invitrogen	#A-21202	IF-1:100
HRP-conjugated goat anti-rabbit IgG	Jackson immunoReseach	111-035-144	1:5000
HRP-conjugated goat anti-mouse IgG	Jackson immunoReseach	115-035-146	1:5000
HRP-conjugated goat anti-mouse IgM	GENETEX	GTX77230	1:5000



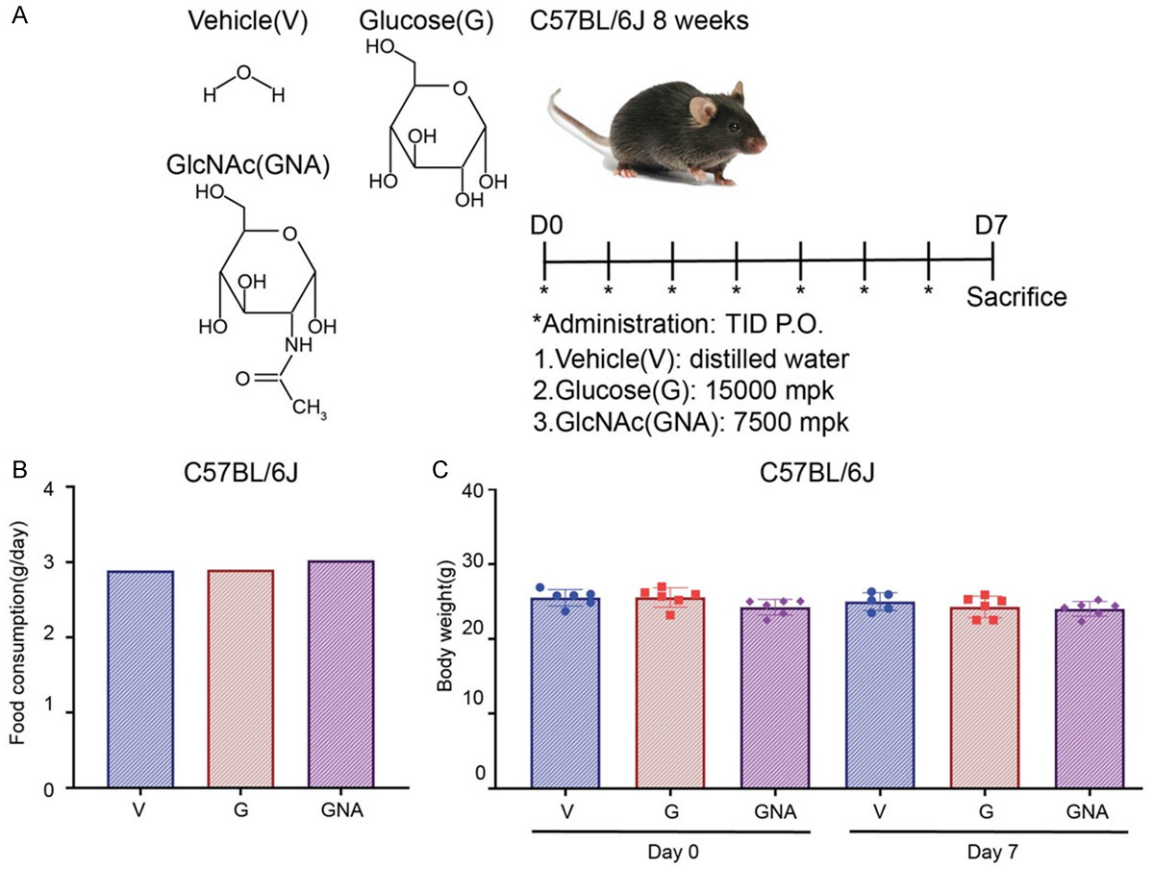
Supplementary Figure 1. Oral sugar uptake has no effects on mice's food consumption and body weight. (A) Experimental scheme for the oral administration of sugar in mice. 8-week-old male C57BL/6JNarl mice were treated with vehicle (water), glucose (G, 15000 mg/kg (mpk)), fructose (F, 15000 mpk), or sucrose (S, 15000 mpk) for 7 days. All sugars were dissolved in water and administered to mice three times daily by oral gavage at 10 μl/g. (B) Average food consumption (g/day) and (C) Body weight (g) of sugar-treated mice on day 0 and day 7. Each dot represents the datum of one mouse. Each group contained 5 mice. Values show mean ± SEM.



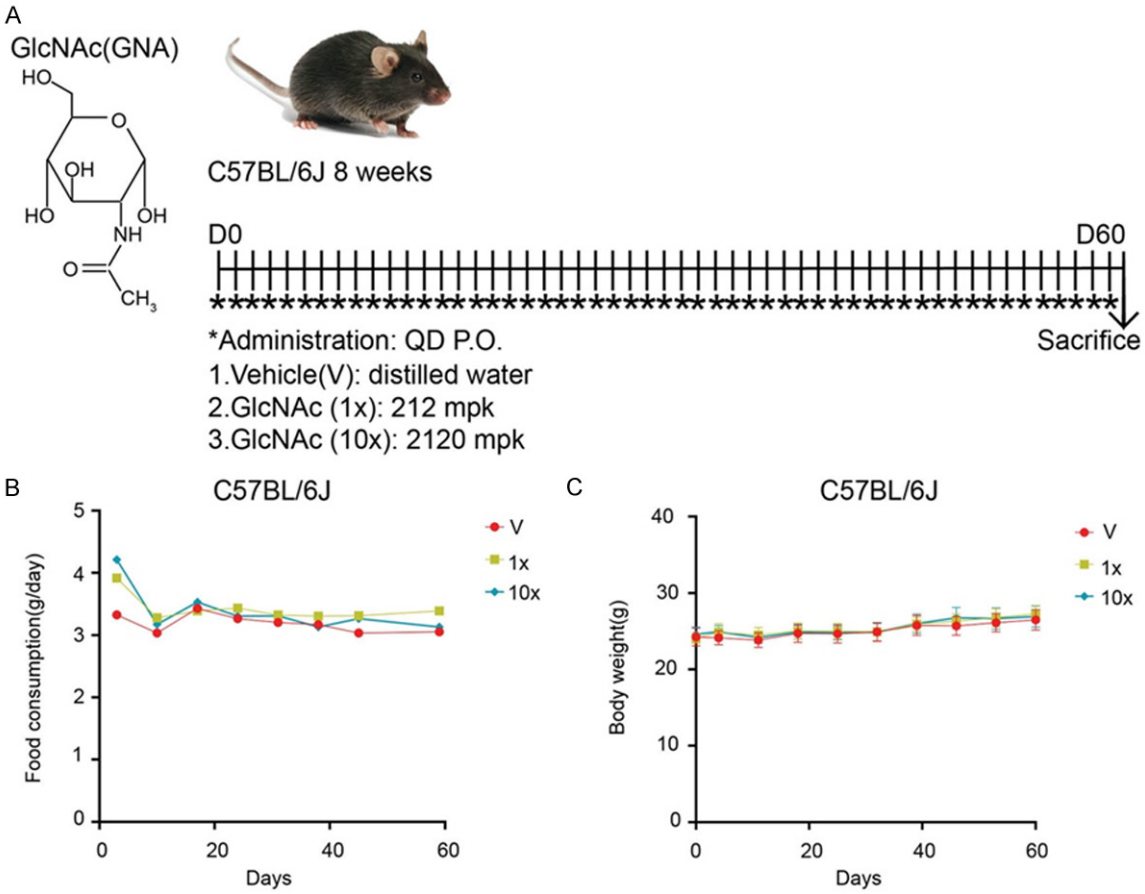
Supplementary Figure 2. The concentration of substrate and product metabolites of PFK and GFAT in 6 organs. Pancreas, brain, liver, lung, kidney, and colon were collected from 10-week-old male C57BL/6JNarl mice. Metabolites, including G6P/F6P (A), glucosamine-6-P (Gln-6P) (B), fructose 1,6 biphosphate (FBP) (C), glutamine (D), and glutamate (E), were extracted from these six organs and quantified by LC-MS analysis. Each group contained 6 mice. Each dot represents the datum of one mouse. Data were presented in nmole/mg. Values show mean ± SEM.



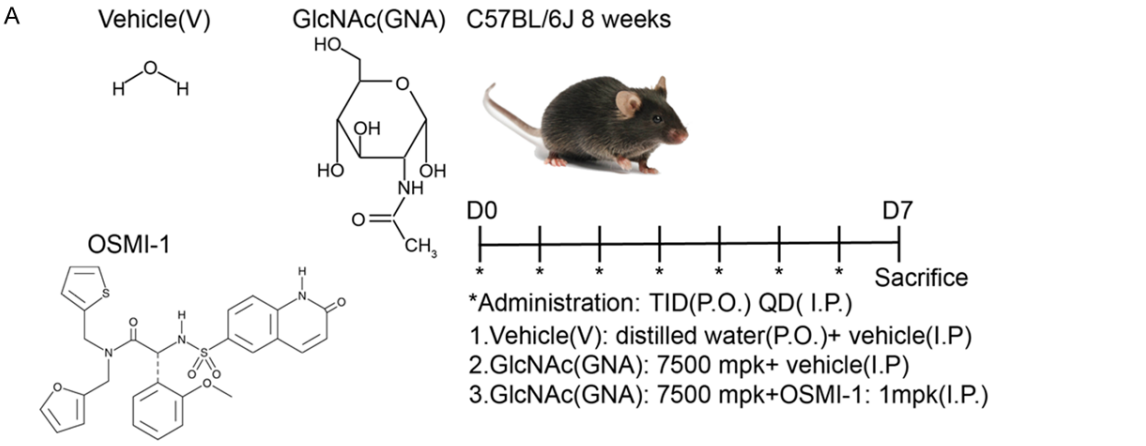
Supplementary Figure 3. Glucose uptake in the pancreas may be converted into more UDP-GlcNAc than other organs. (A) Experimental scheme for U-$^{13}C_6$ glucose tracing assay. 8-week-old male C57BL/6JNarl mice were treated with glucose(U-$^{13}C_6$) (5000 mpk). After glucose(U-$^{13}C_6$) administration, mice were sacrificed at 15, 30, 45, 60, 120, 240 min for blood glucose (mg/dl) analysis (B). Isotope labeled glucose fraction (C), lactate fraction (D), and UDP-GlcNAc ion counts (E) were determined from sera of pancreas, liver, lung, kidney, colon, brain by LC-MS analysis. Each dot represents the datum of one mouse. Each group contained 1 mouse.

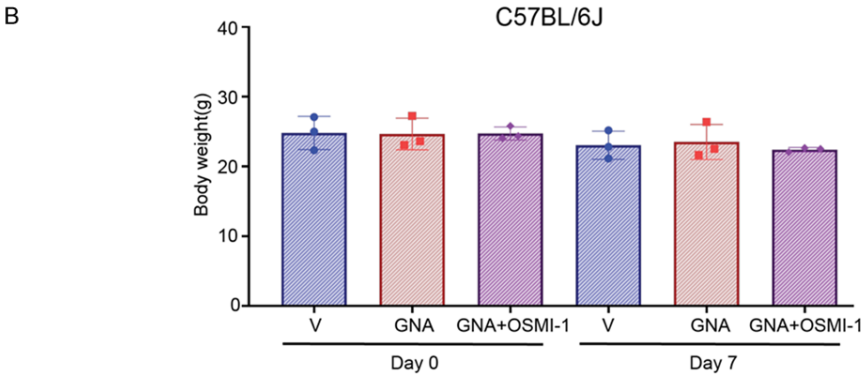


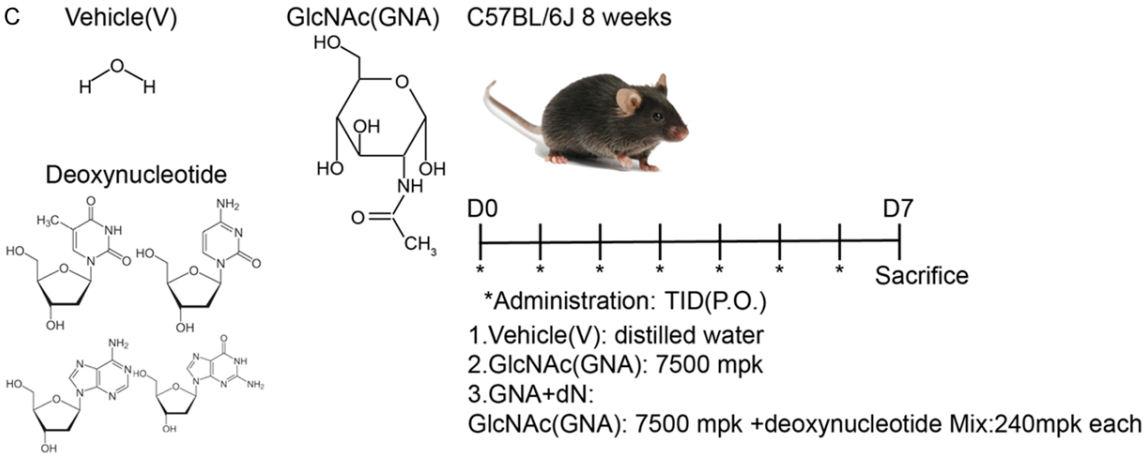
Supplementary Figure 4. Either high sugar or high GlcNAc oral administration has no effects on mice's food consumption and body weight. A. Experimental scheme for the oral administration of sugar in mice. 8-week-old male C57BL/6JNarl mice were treated with vehicle (water), glucose (G, 15000 mpk), or GlcNAc (GNA, 7500 mpk) for 7 days. Glucose and GlcNAc were dissolved in water and administered to mice three times daily by oral gavage at 10 µl/g. B. Average food consumption (g/day). C. Body weight (g) of glucose- or GlcNAc-treated mice on day 0 and day 7. Each dot represents the datum of one mouse. Each group contained 5 mice. Values show mean ± SEM.

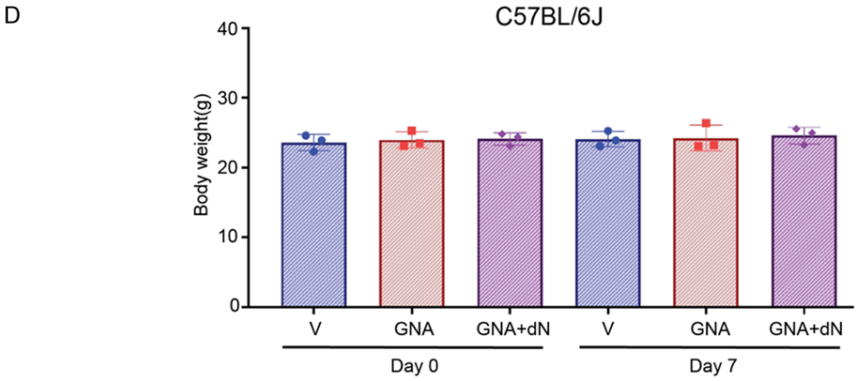


Supplementary Figure 5. Long-term GlcNAc treatment doesn't affect food consumption and body weight in mice. (A) Experimental scheme for the oral administration of sugar in mice. 8-week-old male C57BL/6JNarl mice were treated with vehicle (water), the human equivalent dose of GlcNAc (212 mpk=1X), or 10 times dose (2120 mpk=10X) daily for 60 days. (B) Average food consumption (g/day) and (C) body weight (g) of glucose- or GlcNAc-treated mice on day 0 and day 7. Each dot represents the datum of one mouse. Each group contained 5 mice. Values show mean ± SEM.

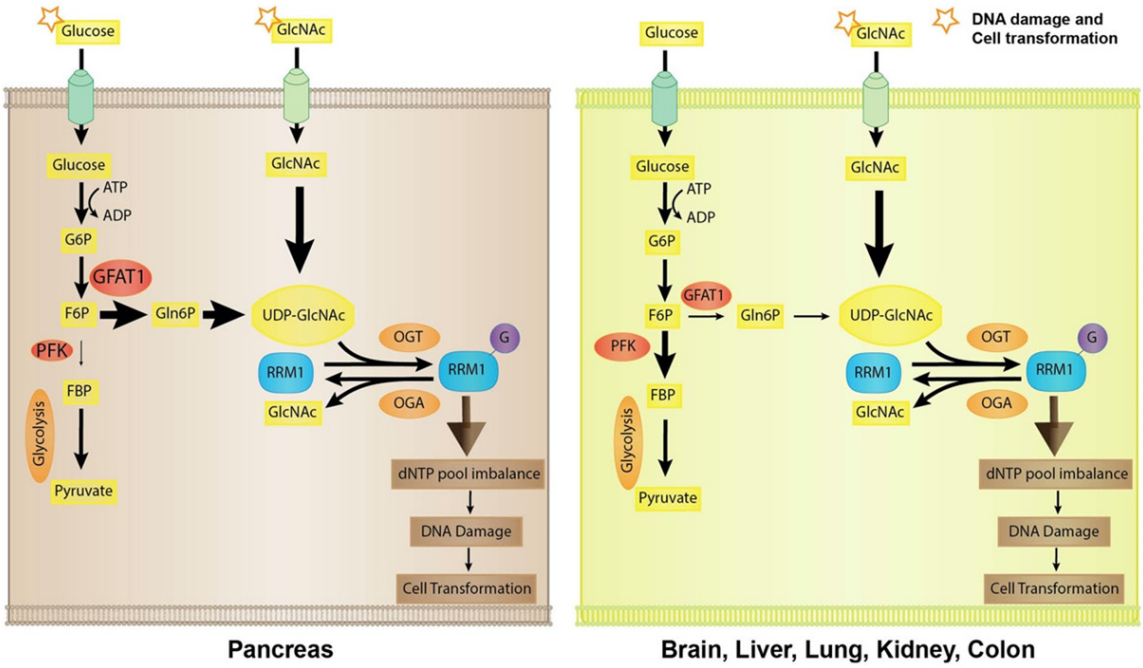

A
Vehicle(V)
GlcNAc(GNA)
C57BL/6J 8 weeks
OSMI-1
D0
D7
Sacrifice
*Administration: TID(P.O.) QD(I.P.)
1.Vehicle(V): distilled water(P.O.)+ vehicle(I.P)
2.GlcNAc(GNA): 7500 mpk+ vehicle(I.P)
3.GlcNAc(GNA): 7500 mpk+OSMI-1: 1mpk(I.P.)


B
C57BL/6J
Body weight(g)
V
GNA
GNA+OSMI-1
Day 0
Day 7

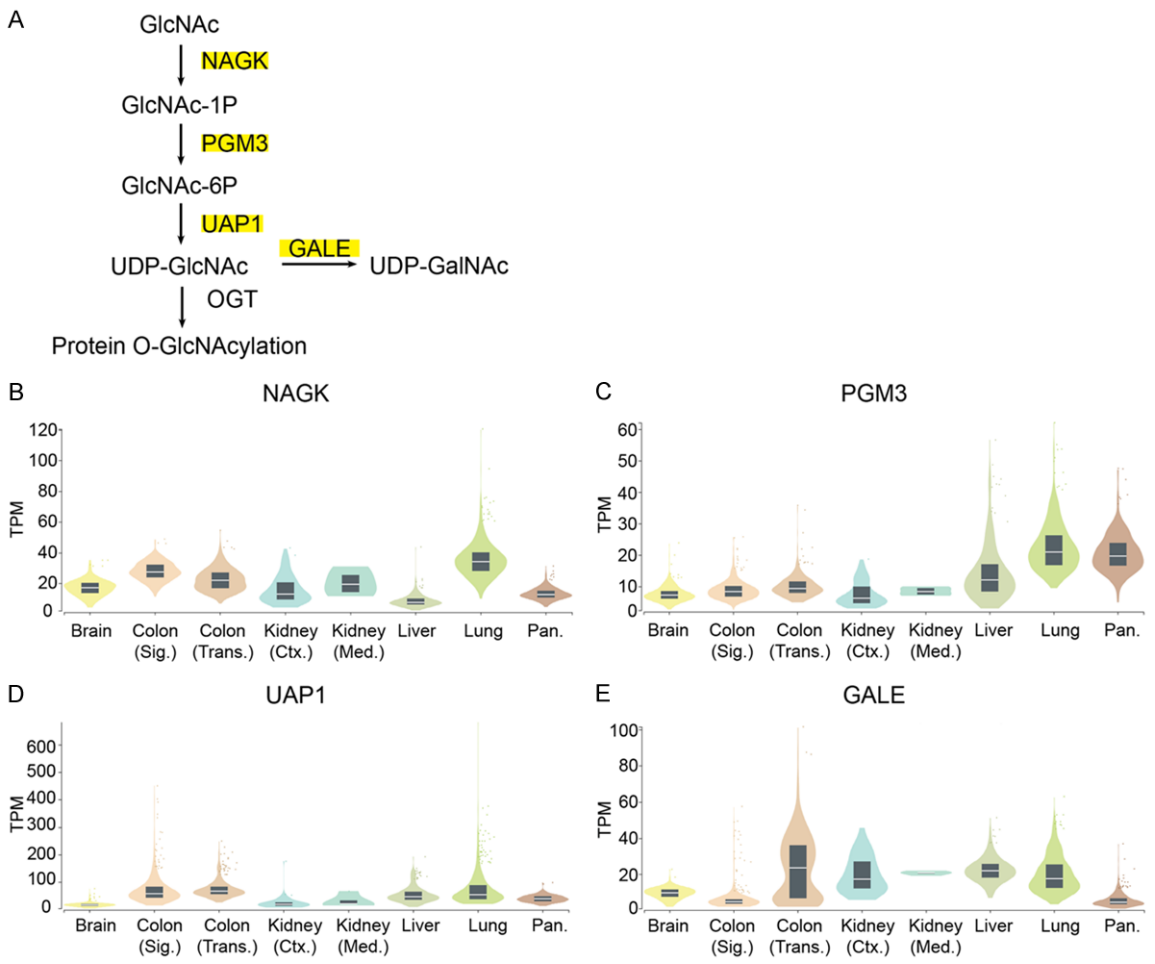

C
Vehicle(V)
GlcNAc(GNA)
C57BL/6J 8 weeks
Deoxynucleotide
D0
D7
Sacrifice
*Administration: TID(P.O.)
1.Vehicle(V): distilled water
2.GlcNAc(GNA): 7500 mpk
3.GNA+dN:
GlcNAc(GNA): 7500 mpk +deoxynucleotide Mix:240mpk each


D
C57BL/6J
Body weight(g)
V
GNA
GNA+dN
Day 0
Day 7

Supplementary Figure 6. Either OSMI-1 intraperitoneal administration or deoxynucleotides oral administration has no effects on body weight in mice. A. Experimental scheme for OSMI-1 intraperitoneal administration in mice. 8-week-old male C57BL/6JNarl mice were treated with vehicle (water) + I.P. solution, GlcNAc (GNA, 7500 mpk) + I.P. solution, or GlcNAc (GNA, 7500 mpk) combined with OSMI-1 (1 mpk I.P.) for 7 days. GlcNAc was dissolved in water and administered to mice three times daily by oral gavage at 10 μl/g. OSMI-1 was dissolved in I.P. solution (10% DMSO, 40% PEG300, 5% tween 80, and 45% saline), and administered to mice once daily by needle at 5 μl/g. B. Average Body weight (g) of GlcNAc and OSMI-1-treated mice on day 0 and day 7. Each dot represents the datum of one mouse. Each group contained 3 mice. Values show mean ± SEM. C. Experimental scheme for deoxynucleotides oral administration in mice. 8-week-old male C57BL/6JNarl mice were treated with vehicle (water), GlcNAc (GNA, 7500 mpk), or GlcNAc (GNA, 7500 mpk) combined with deoxynucleotide (240 mpk P.O.) for 7 days. GlcNAc and deoxynucleotide were dissolved in water and administered to mice three times daily by oral gavage at 10 μl/g. D. Average Body weight (g) of GlcNAc and deoxynucleotide-treated mice on day 0 and day 7. Each dot represents the datum of one mouse. Each group contained 3 mice. Values show mean ± SEM.



Supplementary Figure 7. The proposed model of differential effects of glucose and GlcNAc on DNA damage and cell transformation. High glucose preferentially induces DNA damage and cell transformation in the pancreas. Unlike high glucose that induces pancreas-specific DNA damage, high GlcNAc universally causes DNA damage in the pancreas, brain, liver, lung, kidney, and colon, possibly triggering cell transformation. Owing to higher GFAT activity and lower PFK activity in the pancreas, more glucose is more metabolized to UDP-GlcNAc and increases RRM1-O-GlcNAcylation. O-GlcNAcylated RRM1 triggers ribonucleotide reductase complex disruption, leading to the enzymatic activity reduction and dNTP pool imbalance. High GlcNAc-induced effects are also mediated by O-GlcNAcylated RRM1-mediated dNTP pool imbalance, similar to the action mechanism of high glucose treatment in the pancreas.



Supplementary Figure 8. GlcNAc metabolic-related mRNA expression levels among tissues. (A) Scheme of GlcNAc metabolism. (B-E) The mRNA expression levels of (B) NAGK (ENSG00000124357.12), (C) PGM3 (ENSG00000013375.15), (D) UAP1 (ENSG00000117308.13), and (E) GALE (ENSG00000117308.14) among tissues from GTEx database. TPM: Transcript per million.