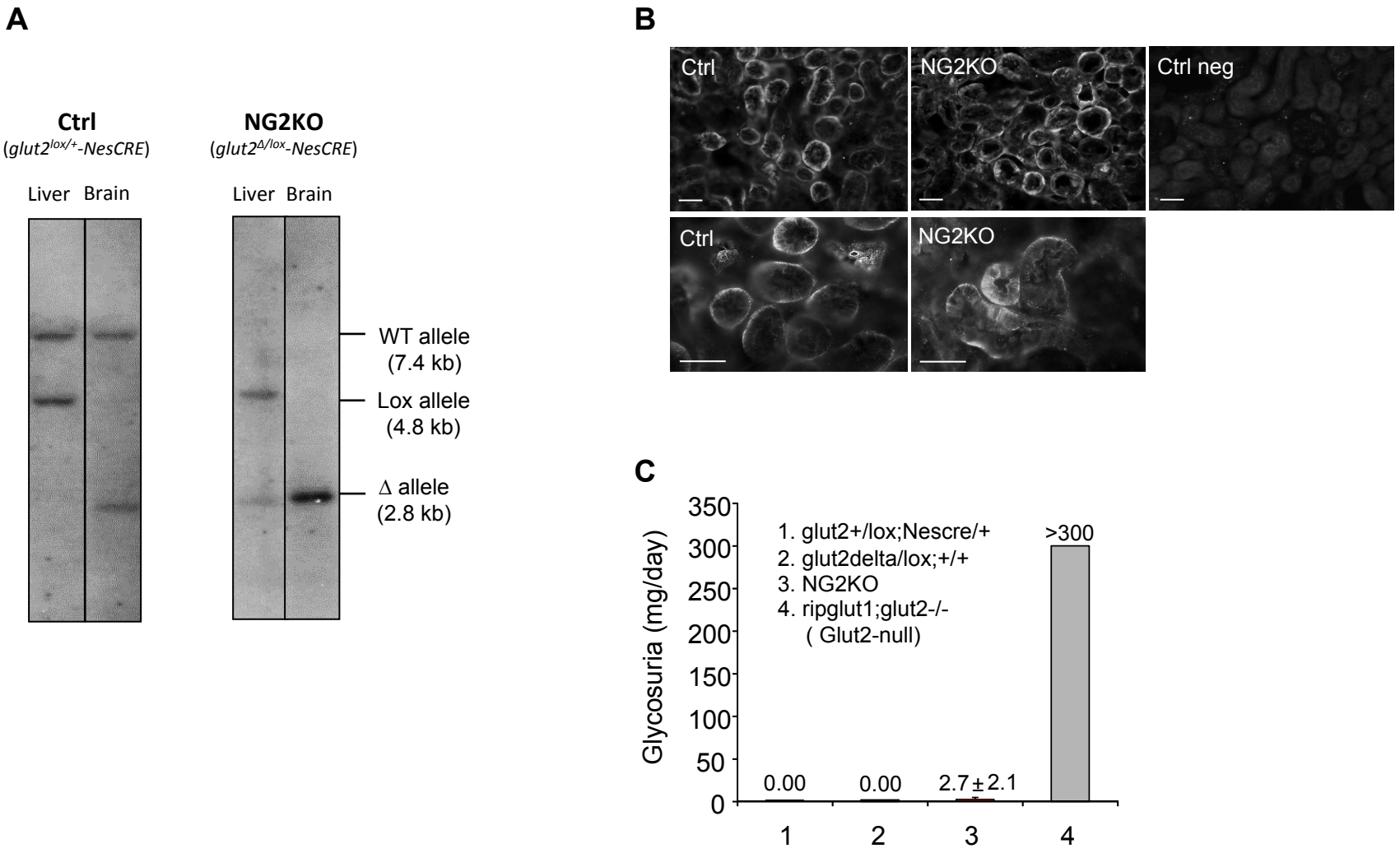

Figure S1:
(A) Southern blot analysis of WT, floxed (Lox) and recombined (Δ) Glut2 alleles in the liver and brain of Ctrl and NG2KO mice. (B) Immunofluorescence detection of GLUT2 in renal cortex of 24 week-old Ctrl and NG2KO mice, and negative control (Ctrl neg; without primary antibody) at 2 different magnification showing proximal tubules with basolateral membrane GLUT2 expression. Scale bars: 20 µm. (C) Daily glucose excretion in mice with the indicated genotype. Data are mean ± SD, n=10

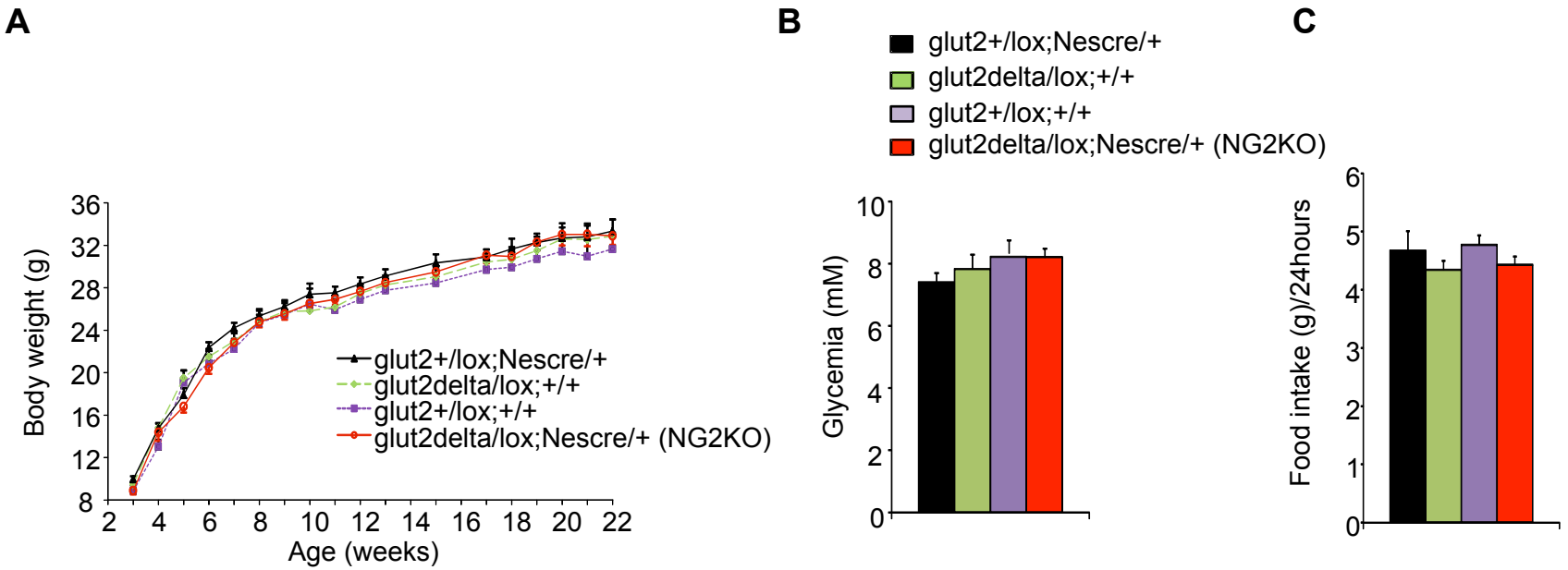

Figure S2: (A) Body weight gain of the *Glut2$^{delta/lox}$;NesCre/+* (NG2KO mice), *Glut2$^{+/lox}$;NesCre/+*, *Glut2$^{delta/lox}$; +/+*, *Glut2$^{+/lox}$; +/+* mice over a 24-week period. (B) Blood glucose in the same 24 week-old mice. (C) 24 hour food intake in the same mice. Data are mean ± SEM, n=10-15.

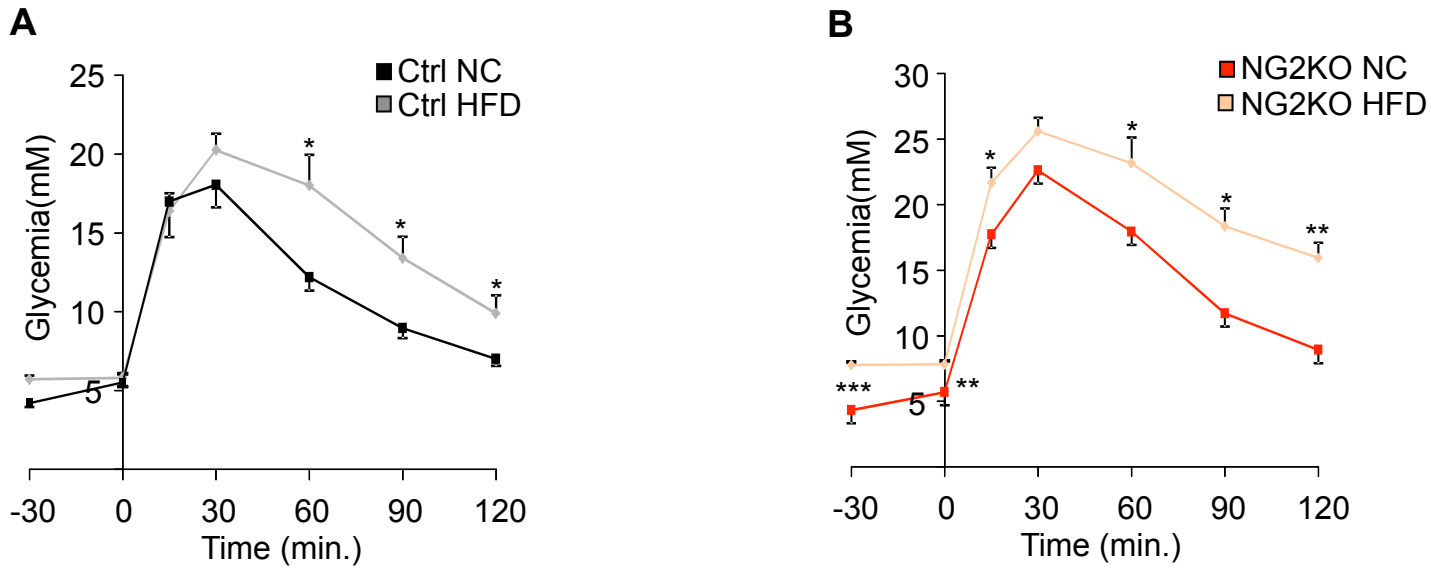

Figure S3: HFD induces glucose intolerance in Ctrl and NG2KO mice. (A) Glucose tolerance tests in 24 week-old NC or HFD fed Ctrl mice. (B) Glucose tolerance tests in 24 week-old NC or HFD fed NG2KO mice. Data are mean ± SEM, n= 7-12. * $p< 0.05$; ** $p<0.01$, ** $p<0.001$. Related to Figures 3 and 4.

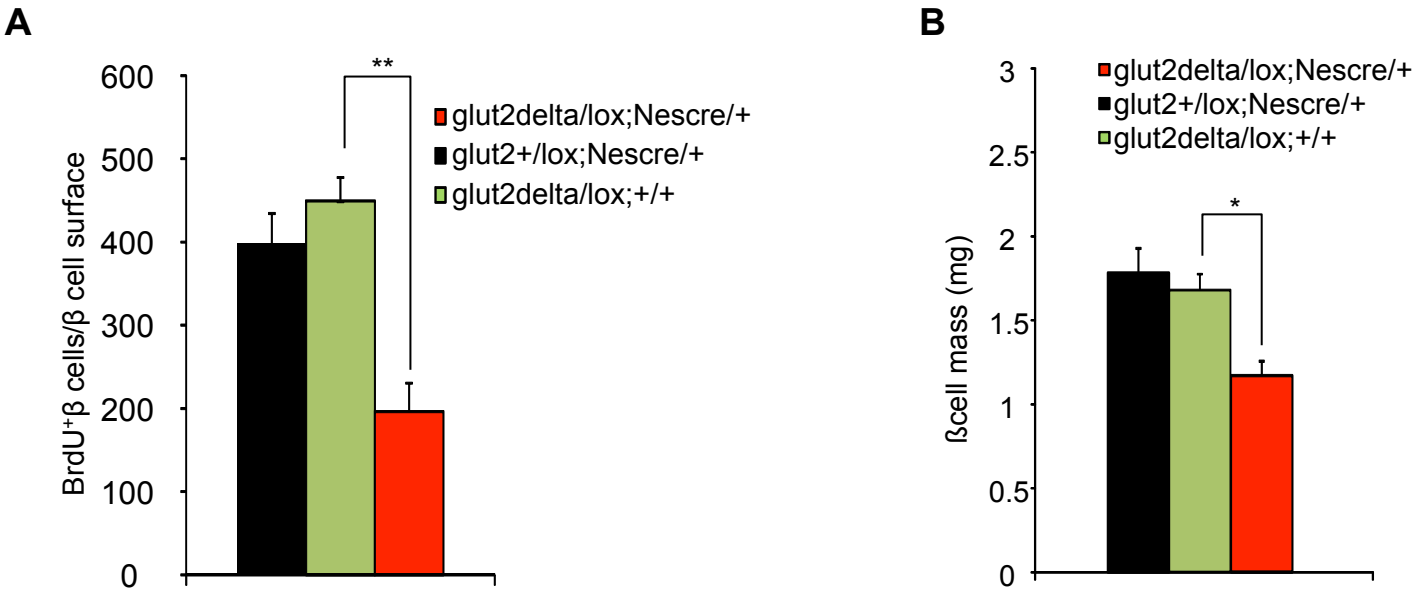

Figure S4

(A) Beta-cell proliferation in 2 week-old NG2KO, Ctrl and *Glut2$^{delta/lox}$; +/+* mice. (B) Beta-cell mass in 9 week-old NG2KO, Ctrl and *Glut2$^{delta/lox}$; +/+* mice. Data are mean ± SEM, n=6-8. * $p< 0.05$; ** $p<0.01$.

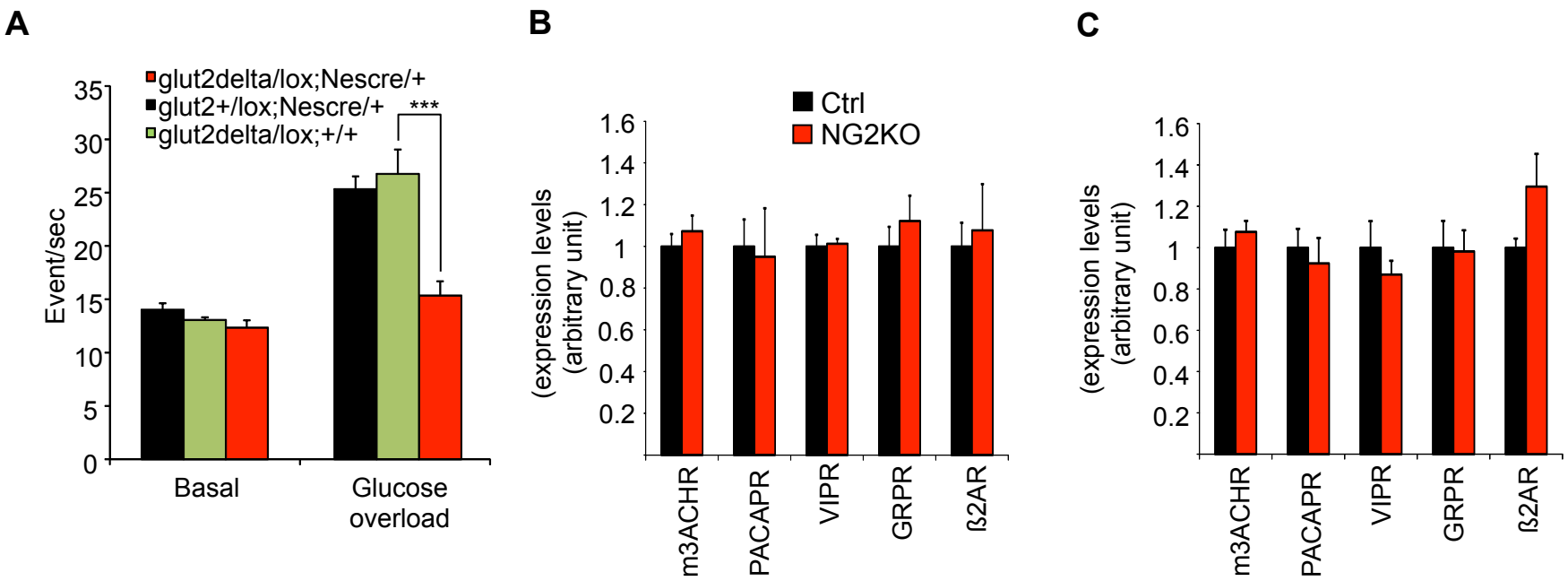

Figure S5

(A) Parasympathetic activity in the basal state and after an i.p. glucose injection in NG2KO, Ctrl and *Glut2*$^{delta/lox}$; +/+ mice. (B) Quantitiative RT-PCR analysis of the expression of the islet receptors for parasympathetic neurotransmitters (m3AchR, PACAPR, VIPR, GRPR) and sympathetic neurotransmitter (β2AR) in 24 week-old NC fed Ctrl and NG2KO mice. (C) same as (A) for 24 week-old HFD fed Ctrl and NG2KO mice. Data are mean ± SEM, n=6-9. *** $p<0.001$.

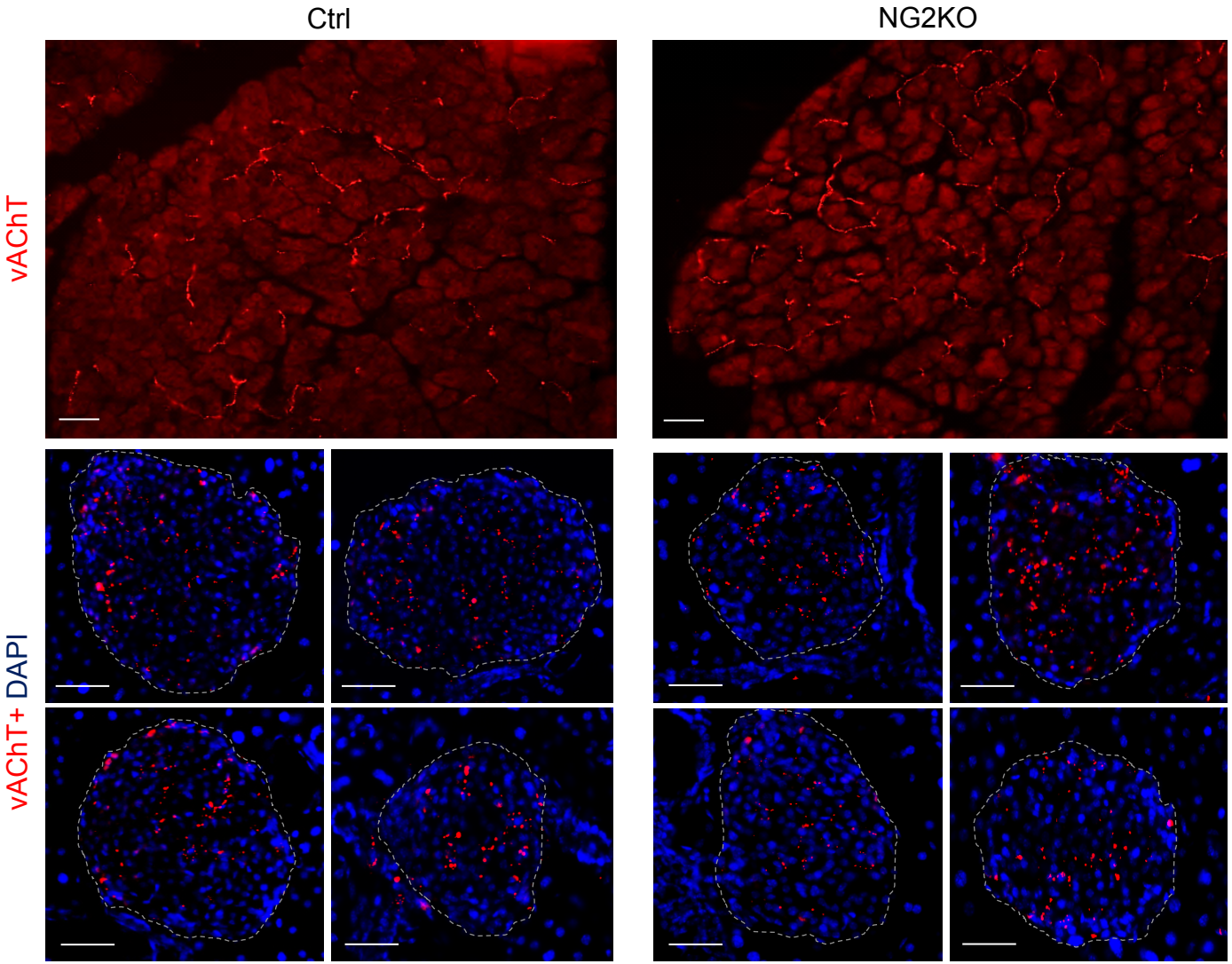

Figure S6: Immunostaining for vesicular acetylcholine transporter (vAChT) in the pancreas from Ctrl and NG2KO mice. Five different pictures taken form different pancreatic fields show that there is no gross difference between parasympathetic innervation of Ctrl and NG2KO islets. Scale bars: 50 µm.

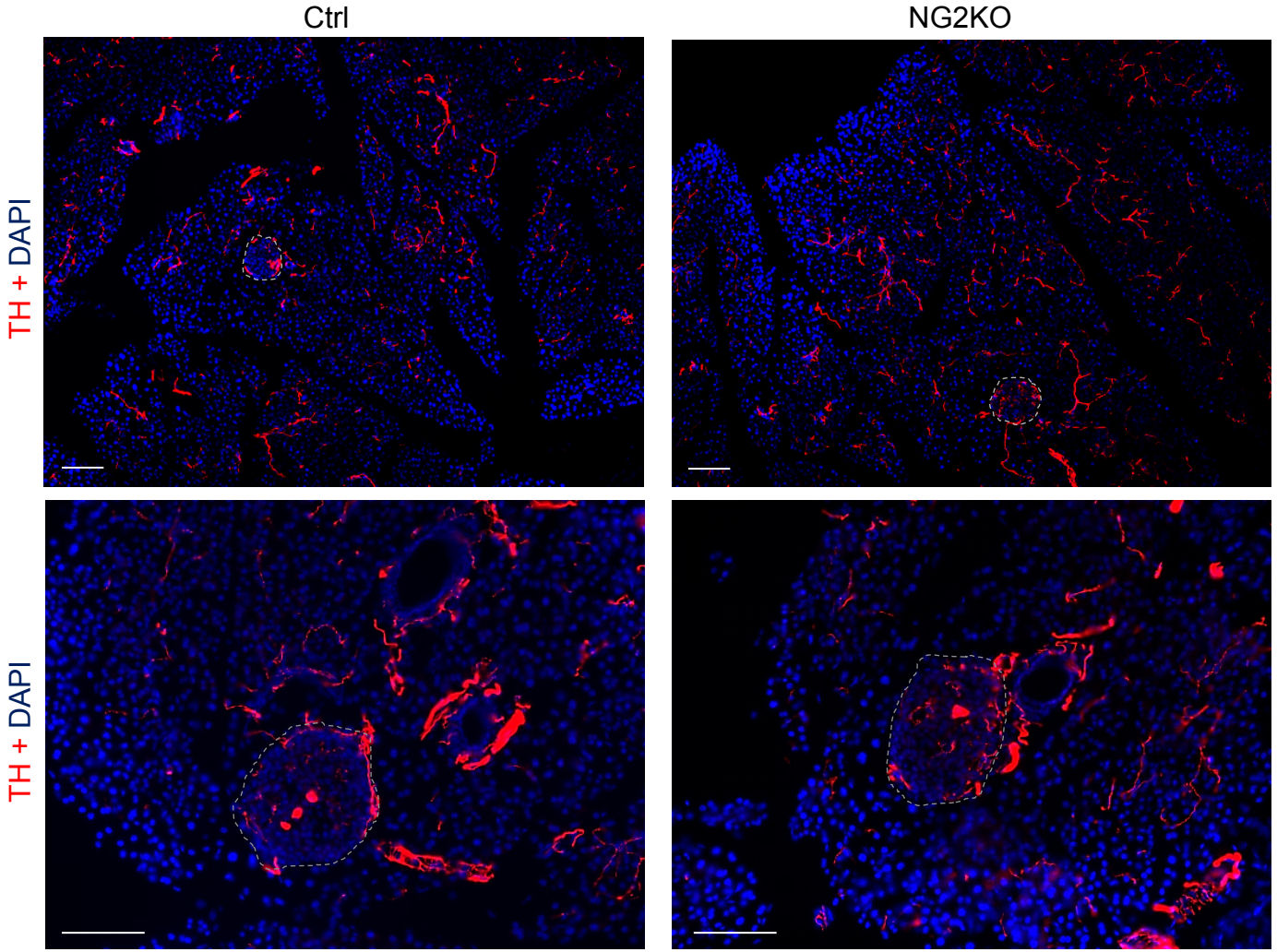

Figure S7: Immunostaining for tyrosine hydroxylase (TH) in the pancreas of Ctrl and NG2KO mice. The distribution of sympathetic fibers in islets and exocrine tissue appears identical in both types of mice. Scale bars: 100 µm.

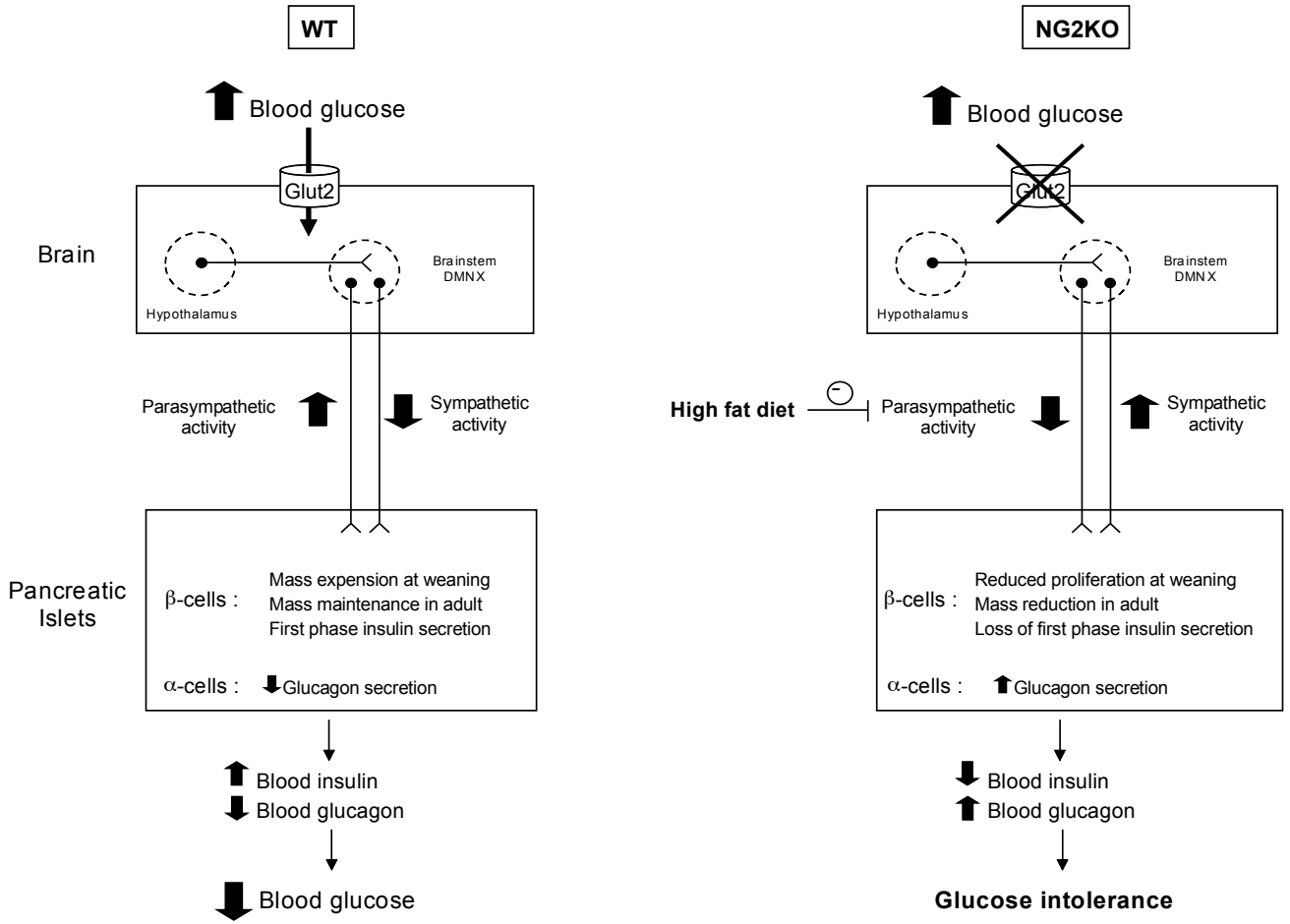

Figure S8

Summary scheme. In WT mice, Glut2 in the nervous system is required for detection of hyperglycemia to activate the parasympathetic activity and to reduce that of the sympathetic nerves. The parasympathetic activity controls beta-cell mass development and maintenance an acute insulin secretion activity. In NG2KO mice, elevated glycemic levels no longer activate the parasympathetic activity nor suppress sympathetic activity. This prevents normal beta-cell mass expansion and maintenance of functional state over time. High fat diet feeding accelerates the appearance of beta-cell dysfunction, probably by impacting on beta-cells physiology and induces deregulated glucagon secretion. The site(s) of Glut2-dependent central glucose sensing involved in the control of autonomic nervous activity are likely located in the hypothalamus and brainstem where Glut2-expressing neurons have been identified.

	1 wks NC	6 wks NC	12 wks NC	24 wks NC	12 wks HFD	24 wks HFD
Ctrl	0.172 +/- 0.006	0.097 +/- 0.007	0.068 +/- 0.008	0.072 +/- 0.004	0.087 +/- 0.006	0.075 +/- 0.005
NG2KO	0.203 +/- 0.028	0.142 +/- 0.014*	0.103 +/- 0.008*	0.121 +/- 0.008**	0.129 +/- 0.013*	0.113 +/- 0.008**

* significantly different from Ctrl

Table S1
Increase alpha to beta cell ratio in the islets of NG2Ko mice. Data are mean ± SEM, n=4-6. * $p< 0.05$; ** $p<0.01$.