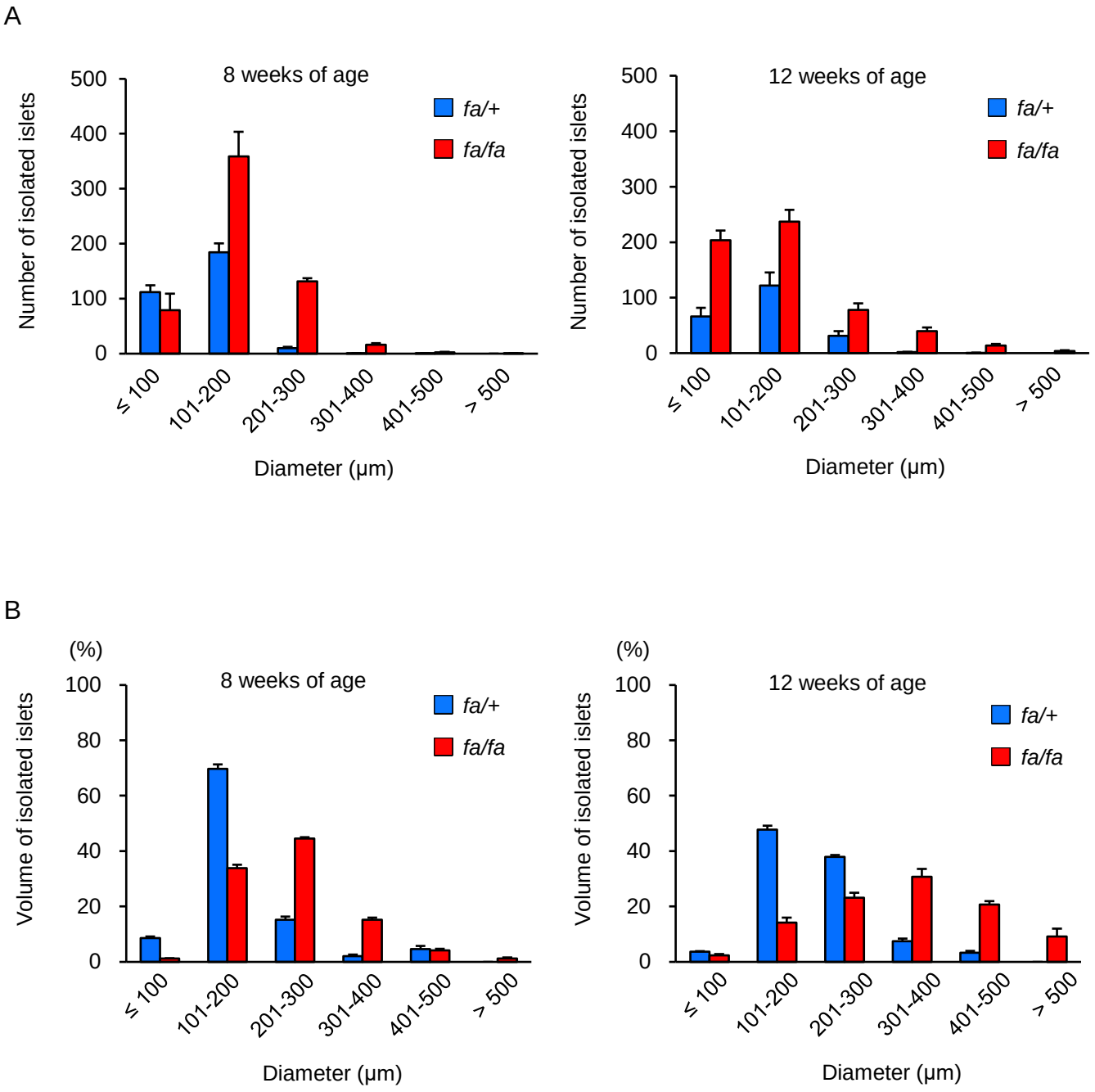
Supplementary Table 1: Pathway analysis of differentially expressed genes among islets of *fa/+* and *fa/fa* rats at 12 weeks of age

KEGG pathway	*P* value
rno04950:Maturity onset diabetes of the young	7.54×10^{-10}
rno04911:Insulin secretion	8.44×10^{-10}
rno04930:Type II diabetes mellitus	1.90×10^{-7}
rno05030:Cocaine addiction	3.66×10^{-6}
rno04974:Protein digestion and absorption	6.72×10^{-5}
rno05031:Amphetamine addiction	7.71×10^{-5}
rno04024:cAMP signaling pathway	5.64×10^{-4}
rno04972:Pancreatic secretion	5.74×10^{-4}
rno04727:GABAergic synapse	9.90×10^{-4}
rno04728:Dopaminergic synapse	0.002092
rno00430:Taurine and hypotaurine metabolism	0.005962
rno05033:Nicotine addiction	0.013114
rno04913:Ovarian steroidogenesis	0.014106
rno00650:Butanoate metabolism	0.016433
rno04923:Regulation of lipolysis in adipocytes	0.017926
rno04713:Circadian entrainment	0.021944
rno04721:Synaptic vesicle cycle	0.022401
rno04922:Glucagon signaling pathway	0.025815
rno04720:Long-term potentiation	0.027575
rno04925:Aldosterone synthesis and secretion	0.029625
rno04723:Retrograde endocannabinoid signaling	0.030139
rno00410:beta-Alanine metabolism	0.031544
rno04142:Lysosome	0.037108
rno00010:Glycolysis / Gluconeogenesis	0.037845
rno05014:Amyotrophic lateral sclerosis (ALS)	0.045215
rno04725:Cholinergic synapse	0.04603
rno01130:Biosynthesis of antibiotics	0.048821

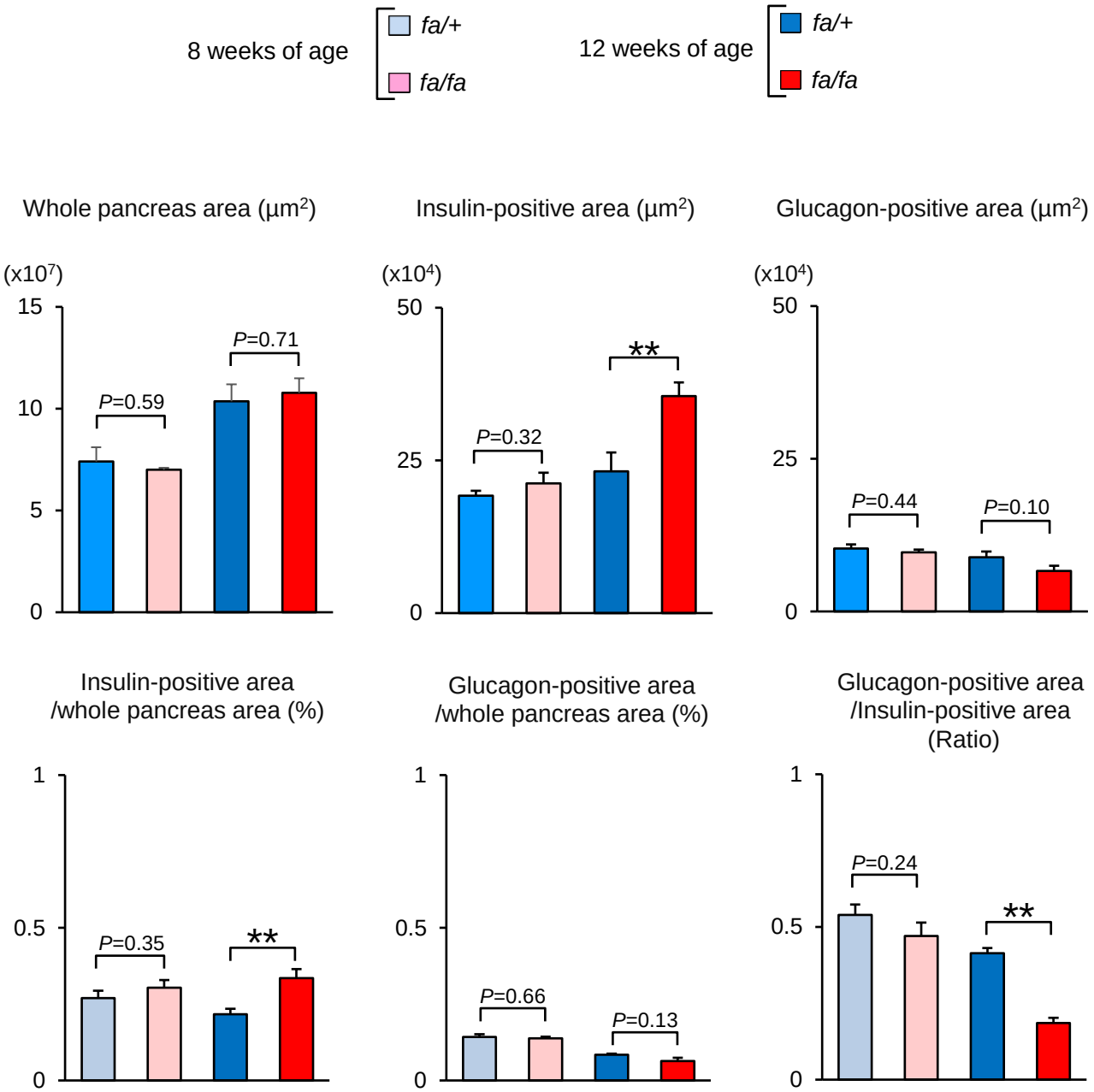
Pathway analysis of differentially expressed genes among islets of *fa/+* and *fa/fa* rats at 12 weeks of age (nominal $P < 0.05$ and fold change > 1.5) was performed by using the Functional Annotation Tool of the DAVID Bioinformatics Resources 6.8.



Supplementary Figure 1: Size distribution of isolated islets of ZFDM rats

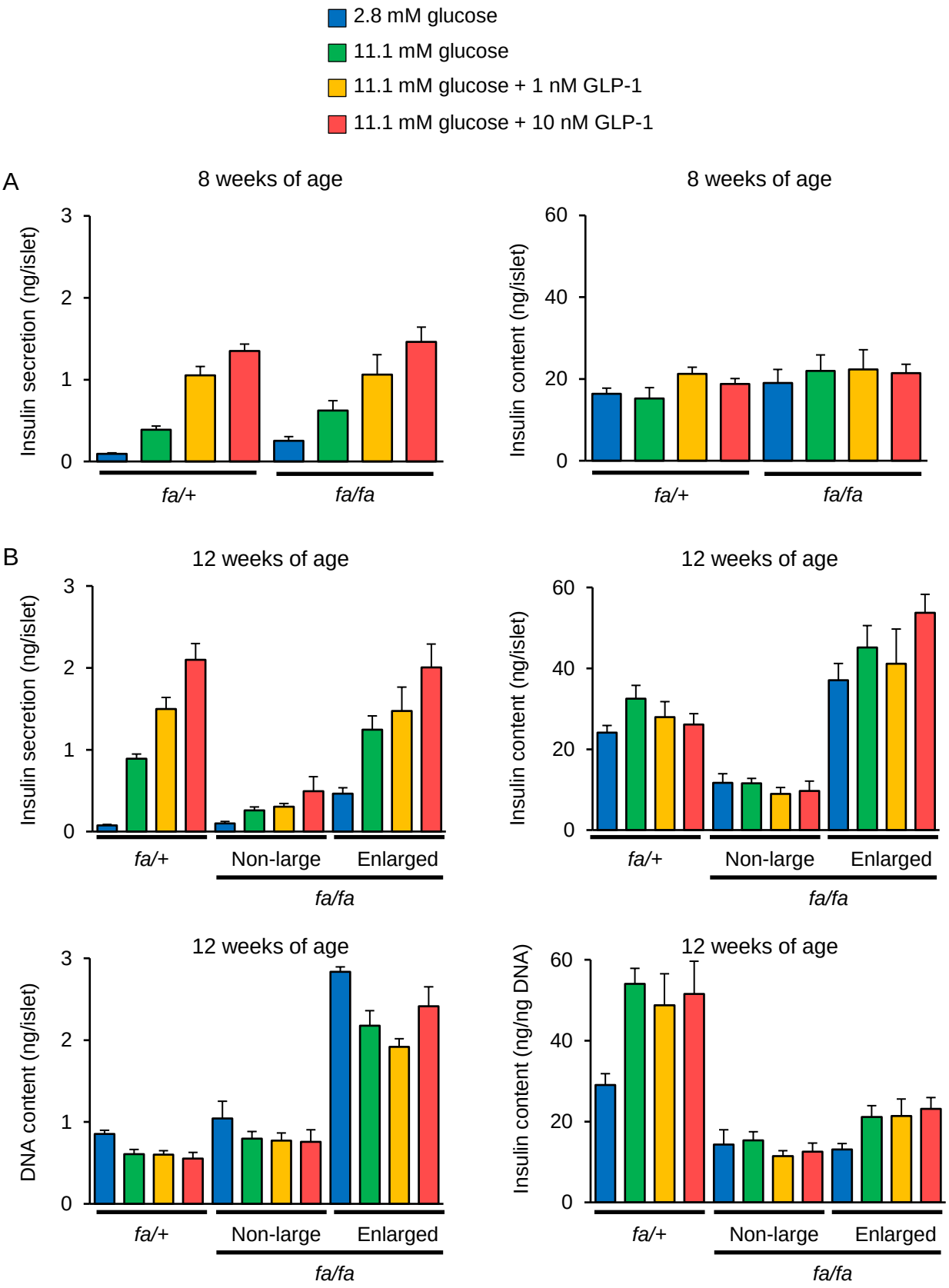
A: The number of isolated islets of ZFDM rats was counted. Diameters of 200-700 islets of each rat were measured with microscopy (n = 8 for *fa*/+ rats; n = 6 for *fa/fa* rats).

B: The volume of isolated islets of ZFDM rats was calculated using diameters of each islets. The data are expressed as means ± SEM.



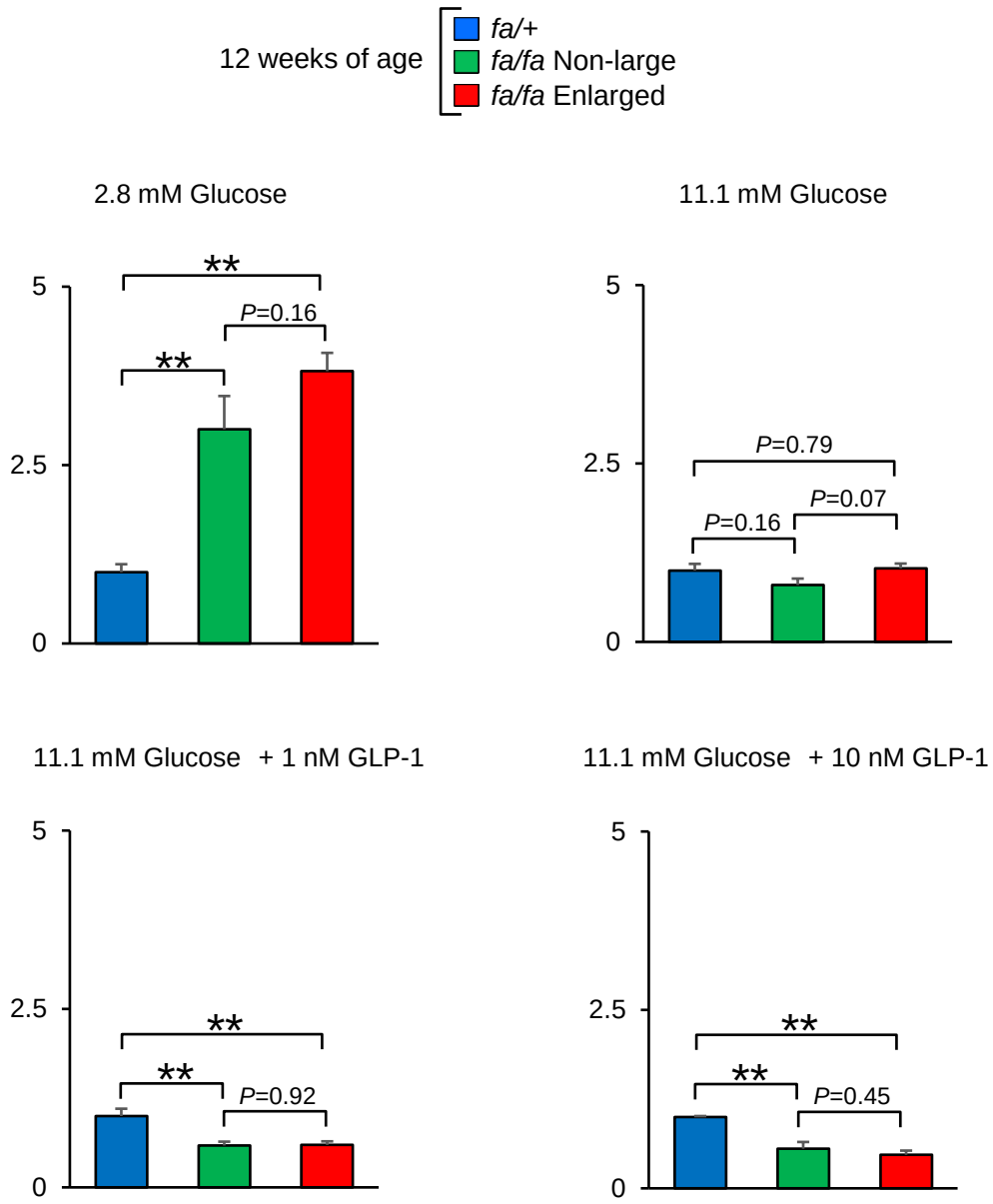
Supplementary Figure 2: The area measurements of whole pancreas, α- and β-cells in ZFDM rats

The ratio of α- or β-cell area in the whole pancreas was calculated by the formula "Total α- or β-cell area divided by whole pancreas area" (6-9 pancreas sections of 3-4 rats for each genotype). The data are expressed as means ± SEM. Holm's method was used for evaluation of statistical significance. $^{**}P < 0.01$.



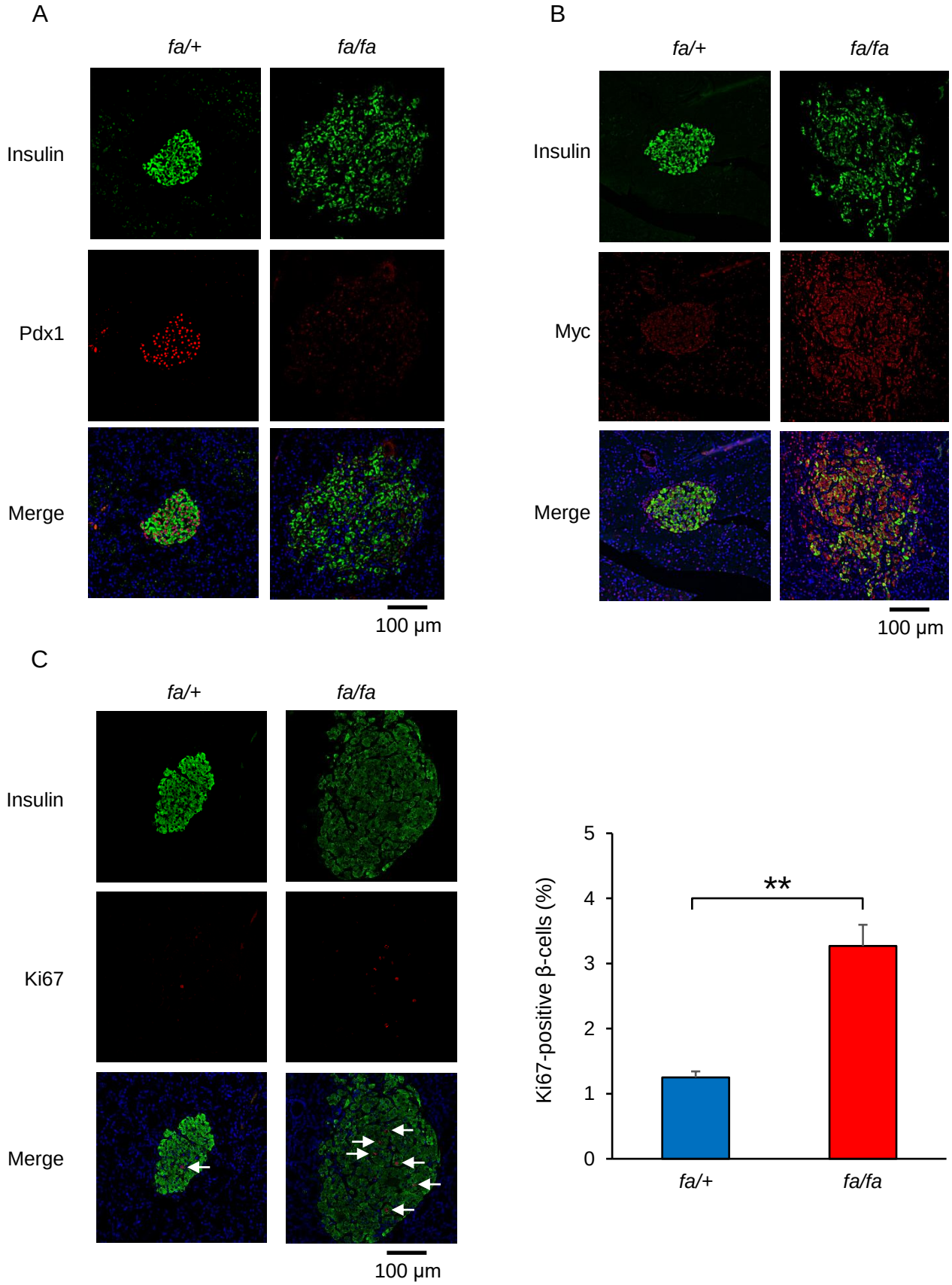
Supplementary Figure 3: Released insulin, insulin content, and DNA content in the islets of ZFDM rats

The islets were stimulated with glucose and GLP-1 at 8 (A) and 12 (B) weeks of age (n = 5-8). The data are expressed as means ± SEM.



Supplementary Figure 4: Comparison of insulin secretion among islets of *fa/+* and *fa/fa* rats at 12 weeks of age

Insulin secretion is presented as fold-change relative to that of fa/+ rats (n = 5-8). The data are expressed as means ± SEM. Holm's method was used for evaluation of statistical significance. $^{**}P < 0.01$.

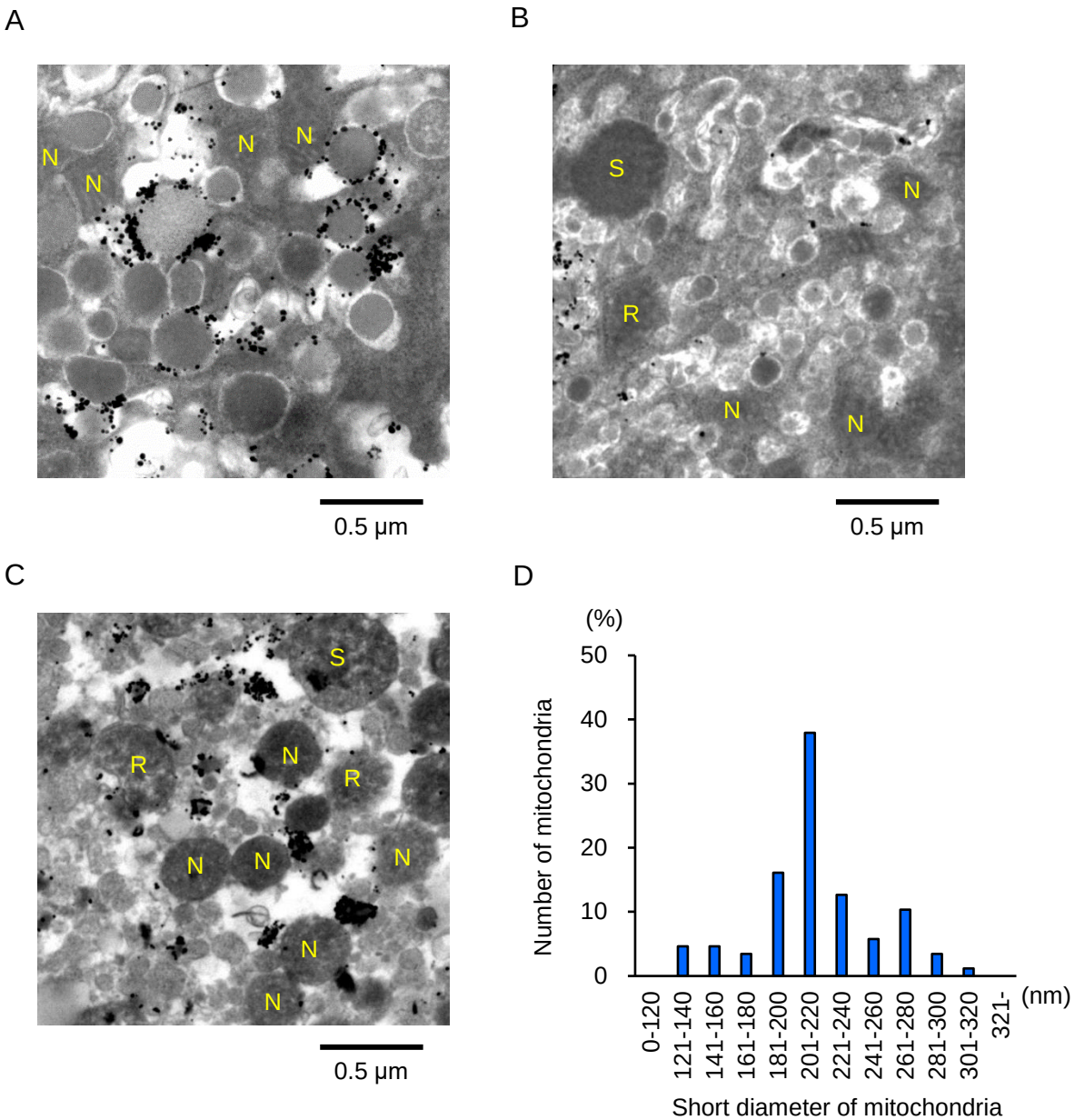


Supplementary Figure 5: Immunostaining of pancreas

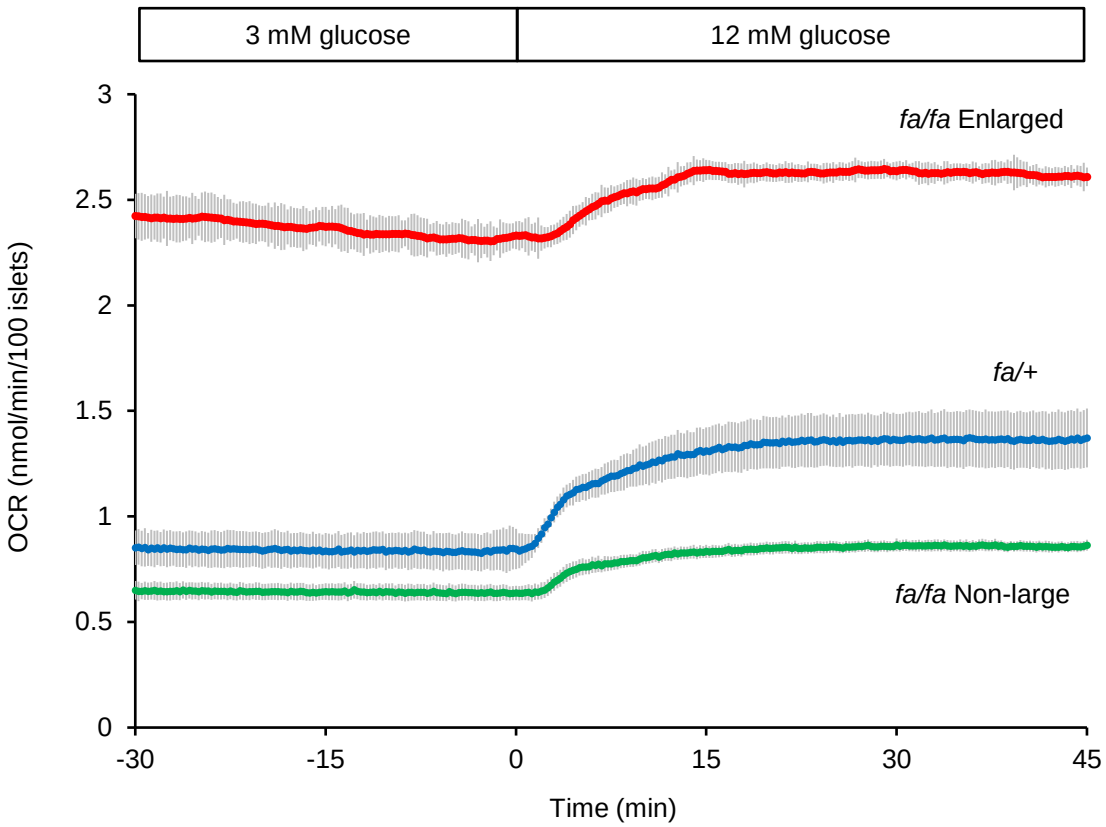
A: Immunostaining of ZFDM pancreas for insulin (green), Pdx1 (red), and DAPI (blue).

B: Immunostaining of ZFDM pancreas for insulin (green), Myc (red), and DAPI (blue).

C: Immunostaining of ZFDM pancreas for insulin (green), Ki67 (red), and DAPI (blue). White arrows indicate Ki67 and insulin double-positive cells. The data are expressed as means ± SEM (n = 4). Welch's method was used for evaluation of statistical significance. $^{**}P < 0.01$.



Supplementary Figure 6: Morphology of the mitochondria in β-cells of ZFDM rats
Morphological examination of mitochondria was performed by transmission electron microscopy.
A: *fa*/+, B: *fa/fa* Non-large islets, C: *fa/fa* Enlarged islets, D: Size distribution of the mitochondria in β-cells of *fa*/+ rats.
The black dots represent gold particles conjugated with a secondary antibody used for detection of the primary anti-insulin antibody.



Supplementary Figure 7: Oxygen consumption rate (OCR) of ZFDM islets
The values of OCR were measured under low glucose (3 mM) and high glucose (12 mM) conditions (n = 3-4). The data are expressed as means ± SEM.