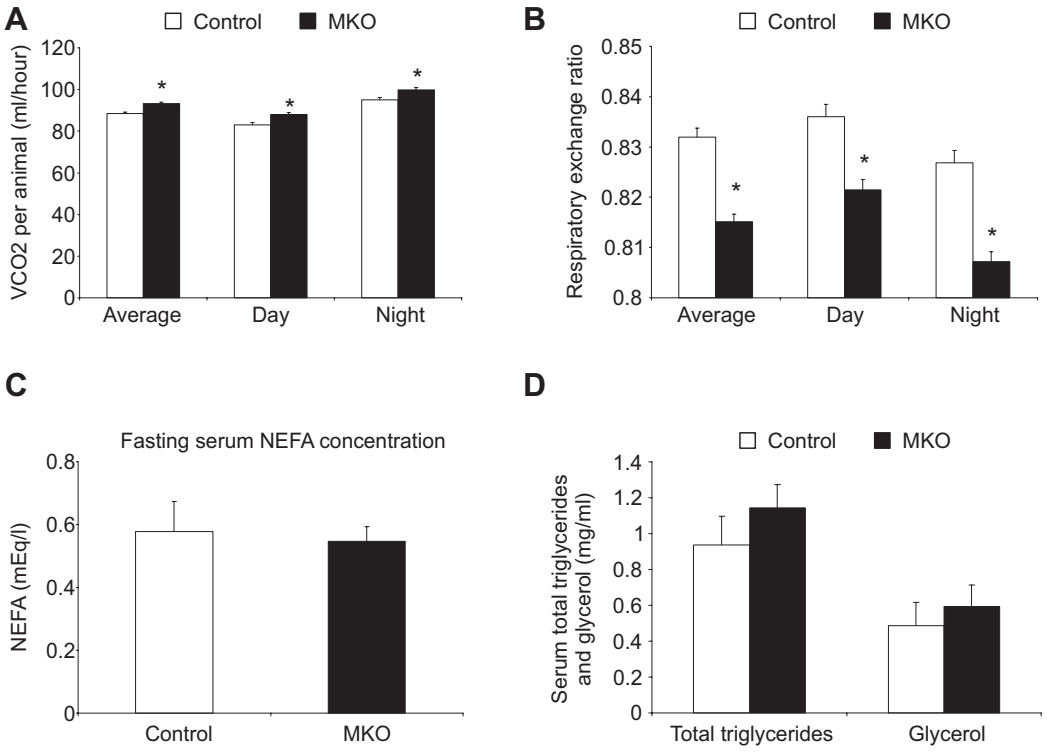
Supplemental Fig. S1



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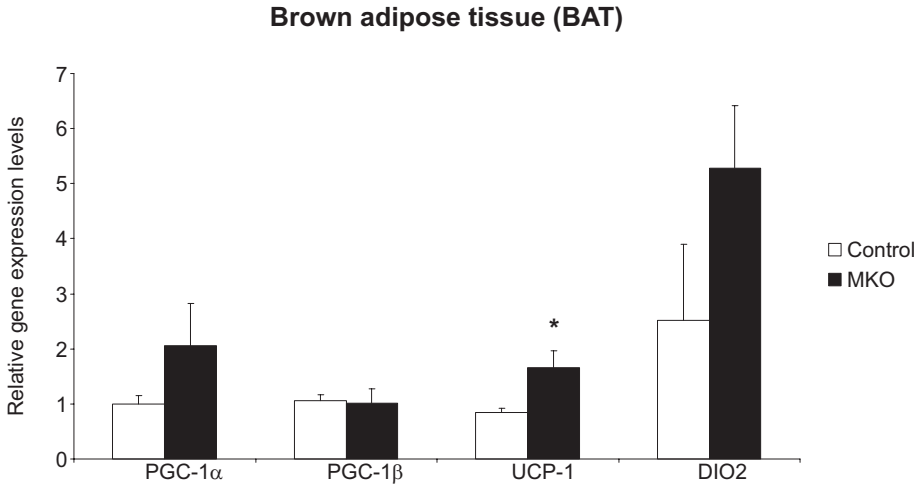

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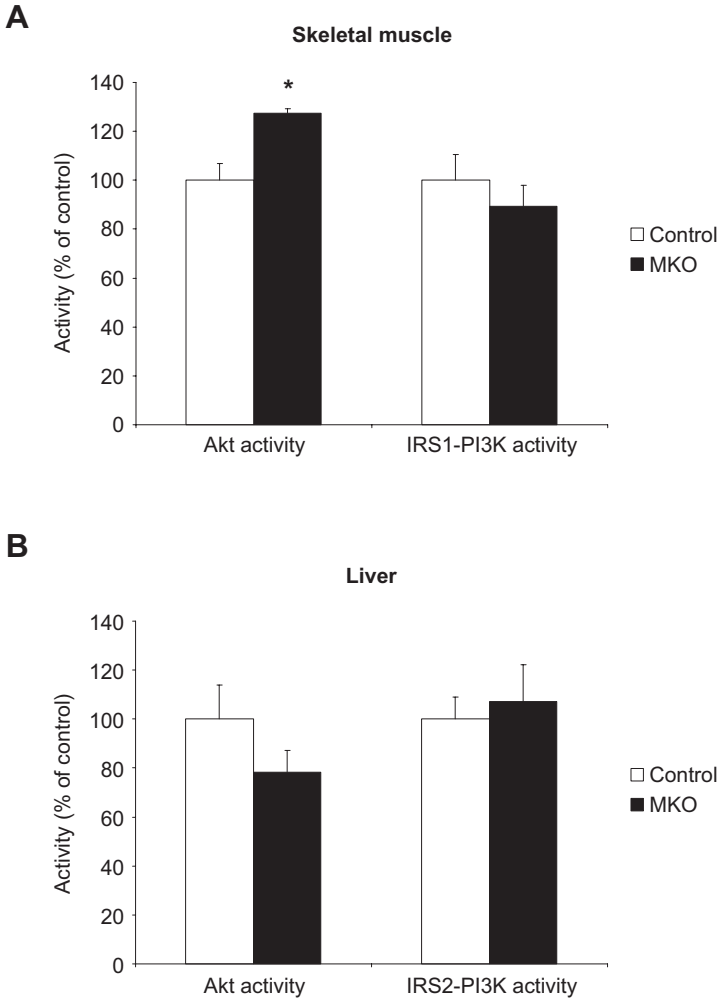

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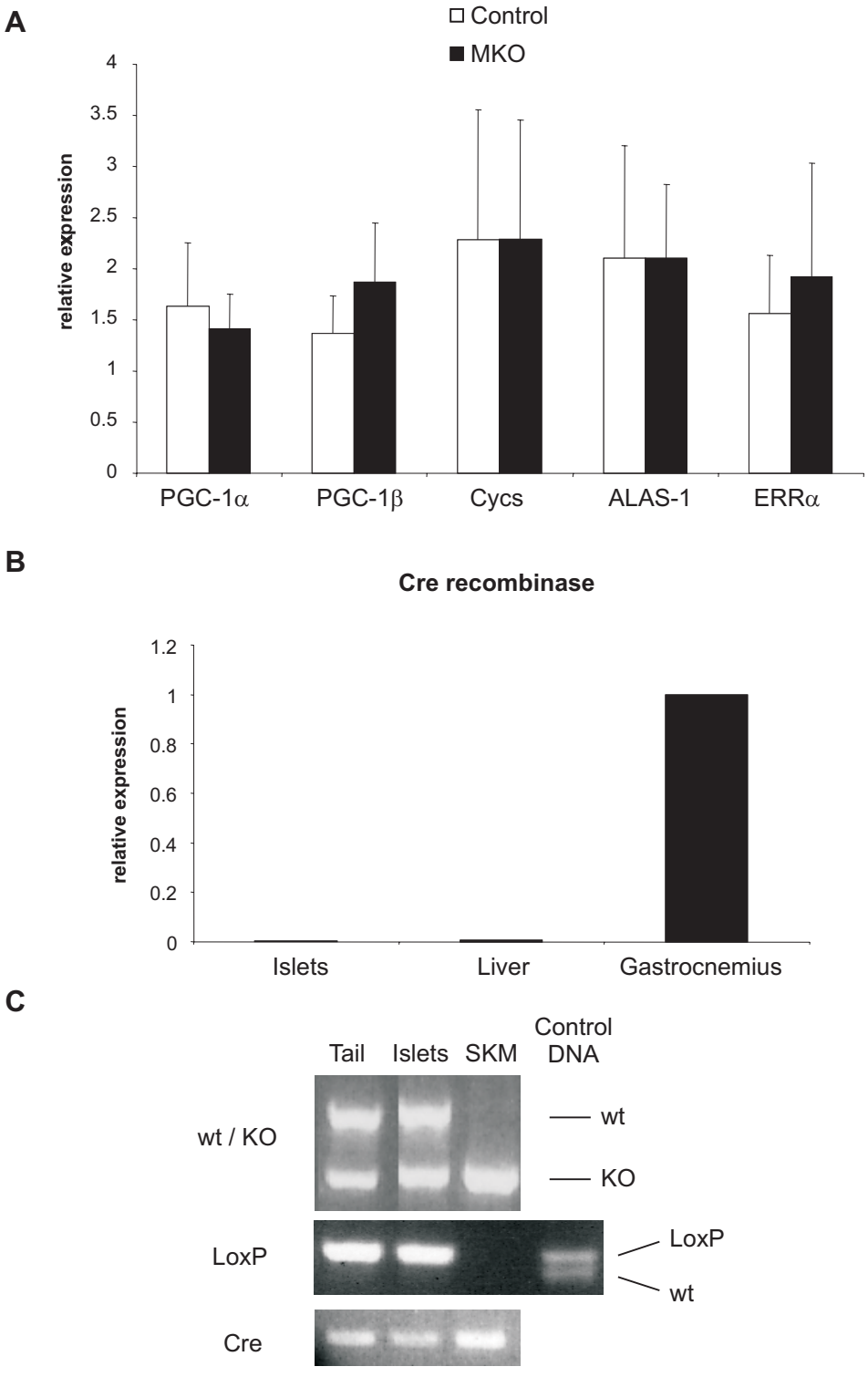

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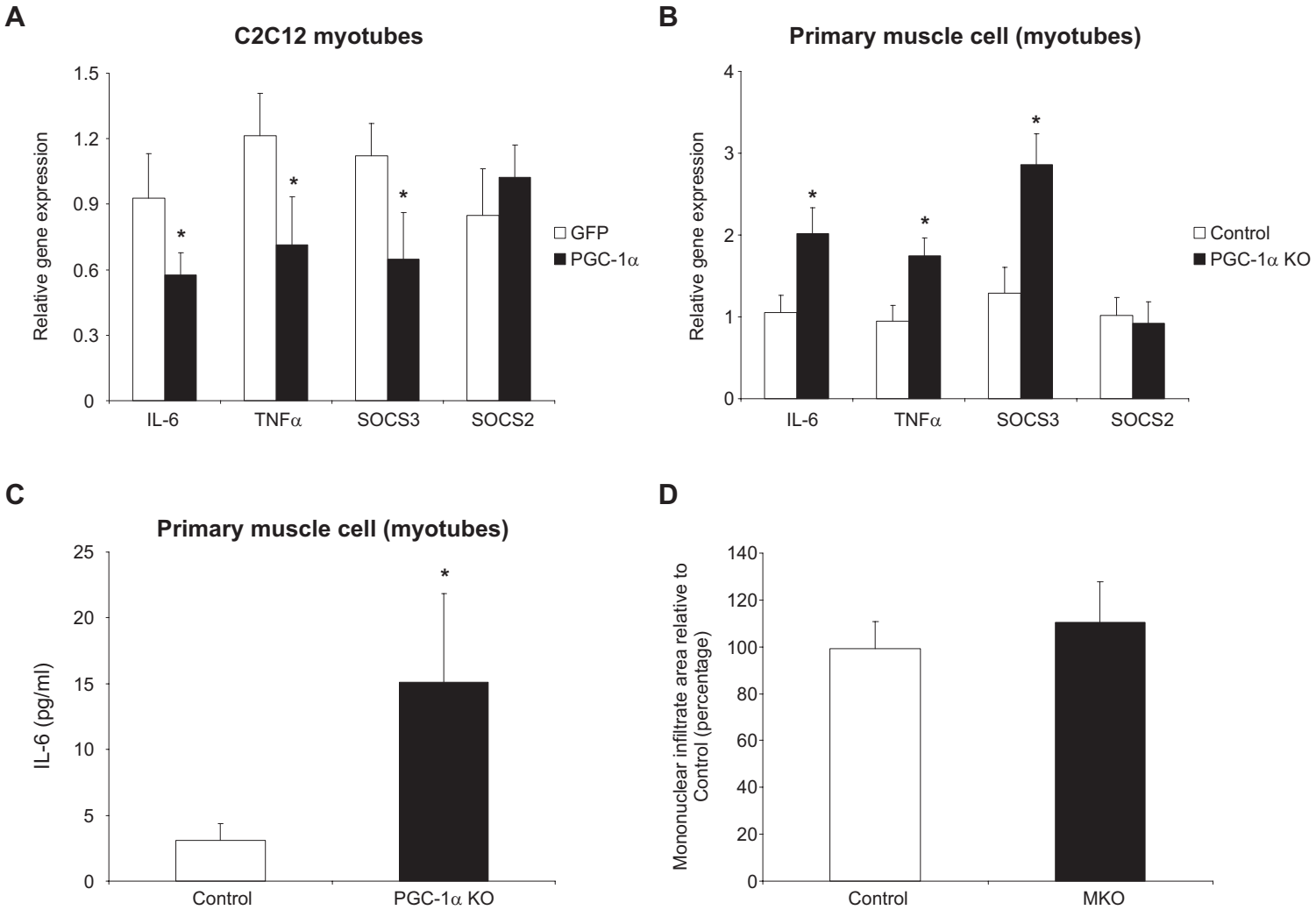

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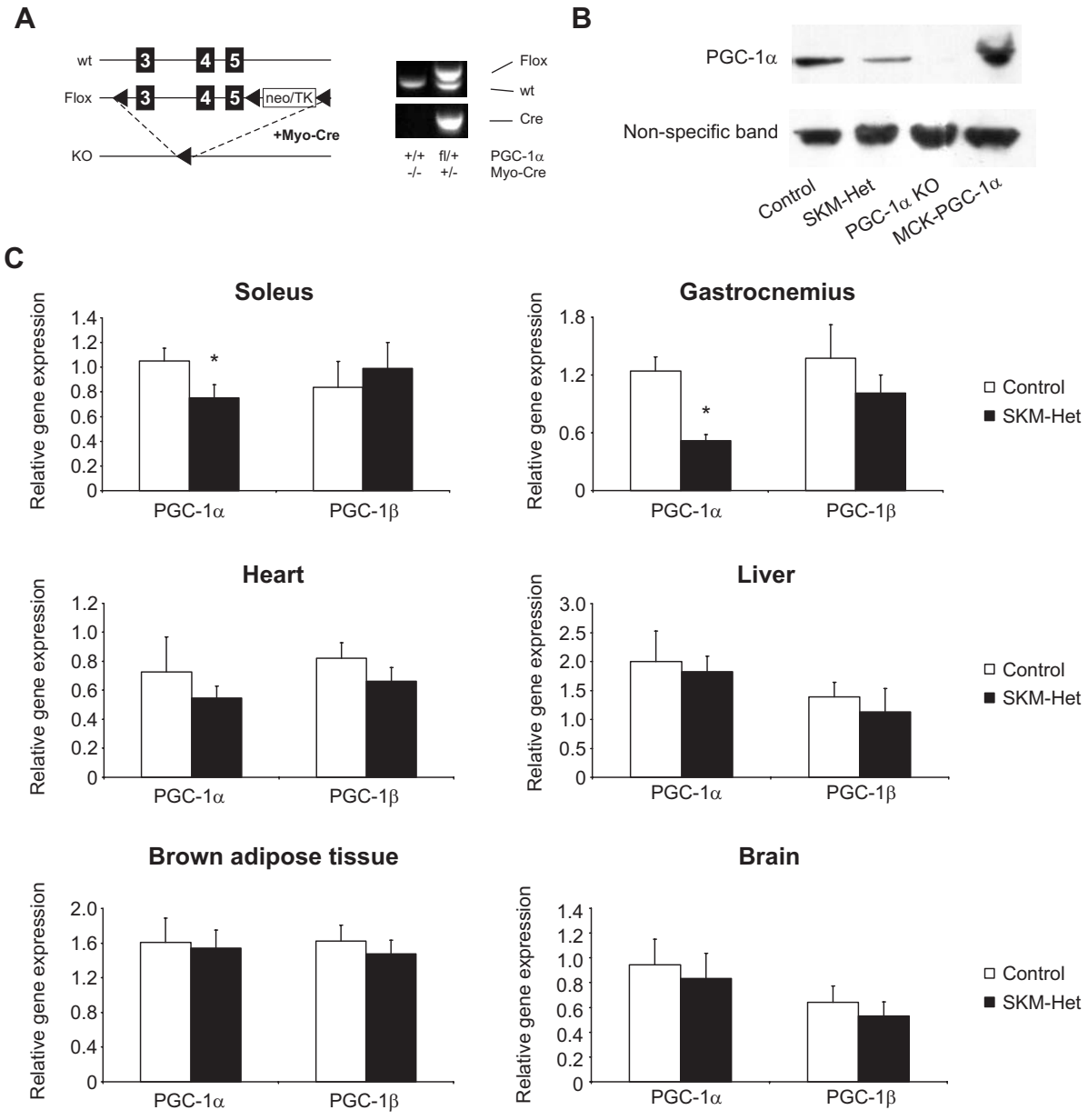

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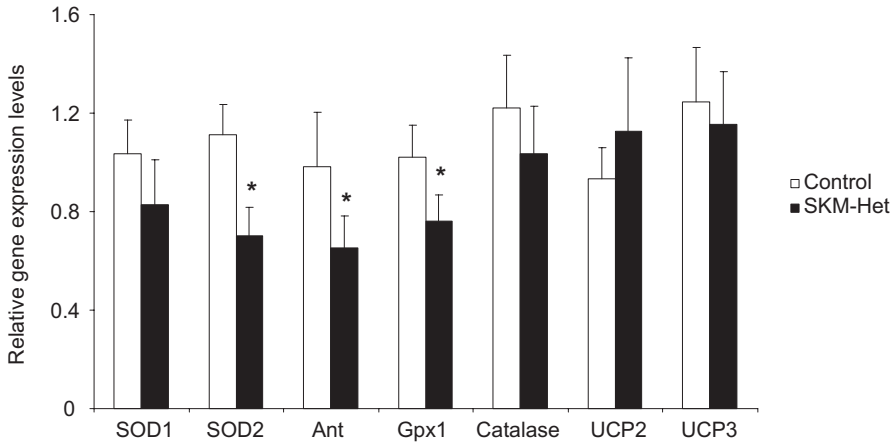

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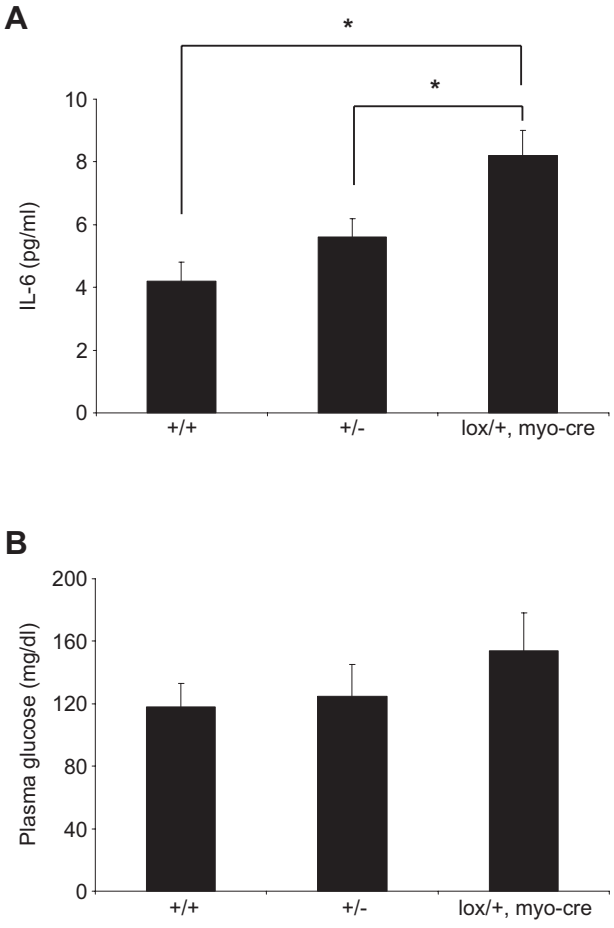

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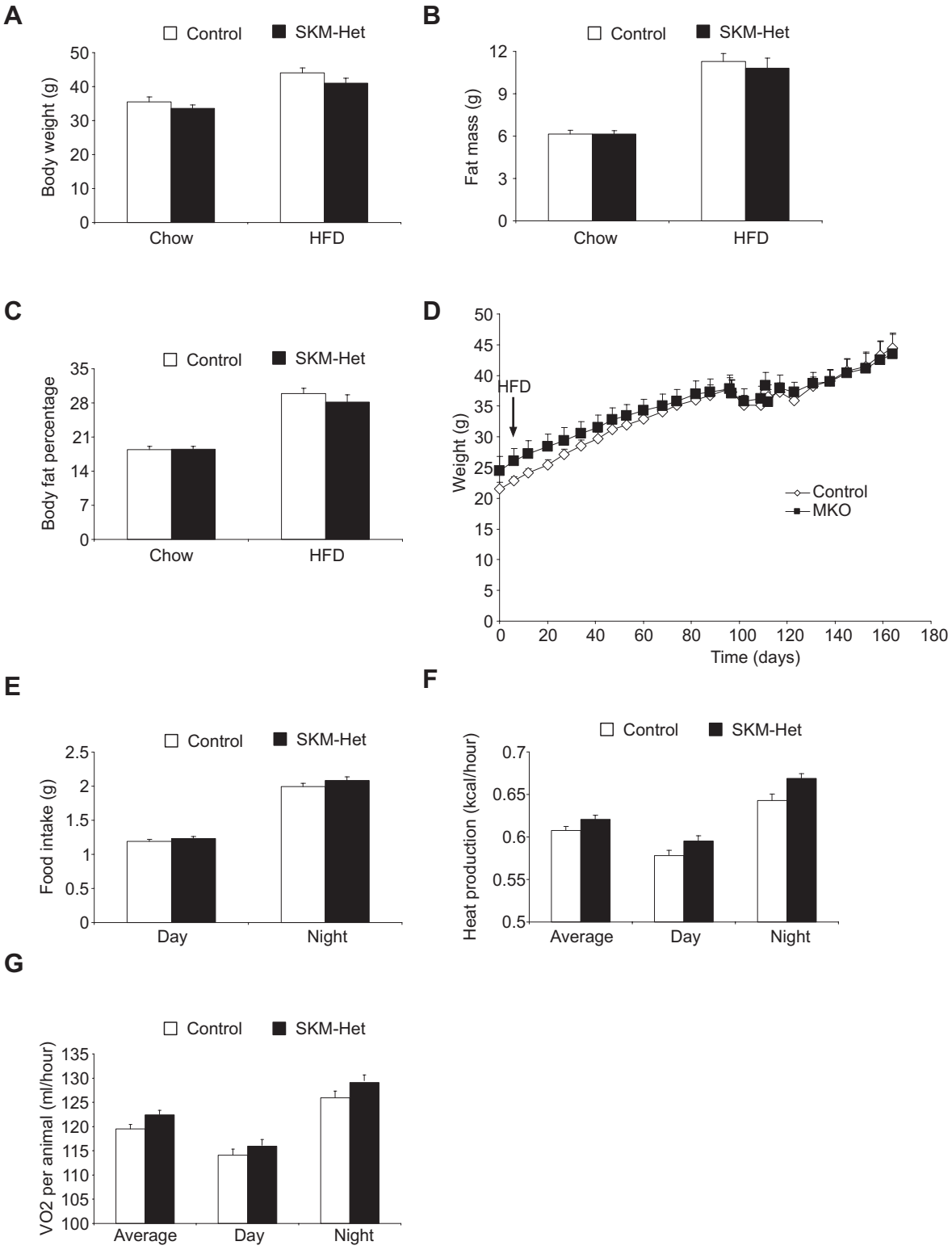

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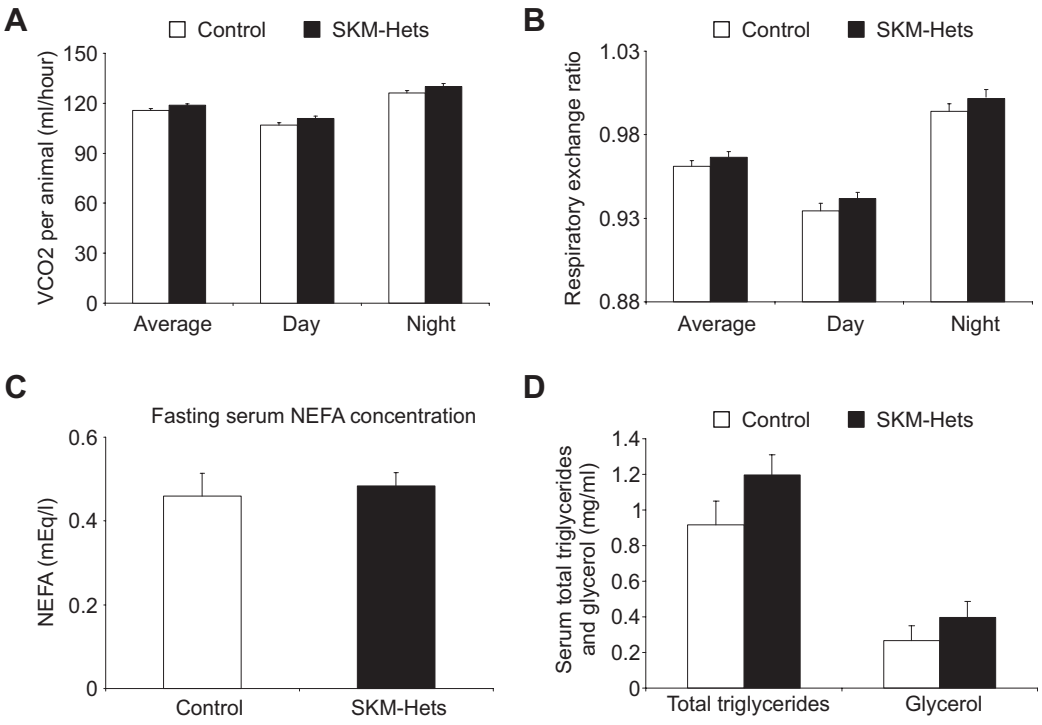

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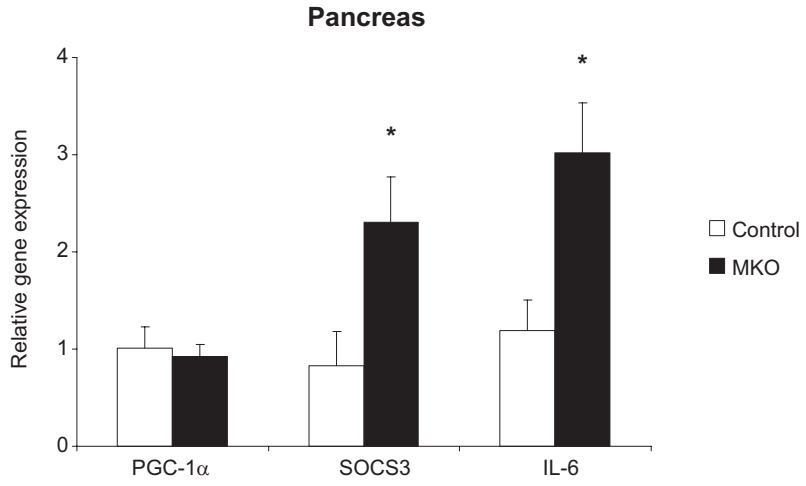

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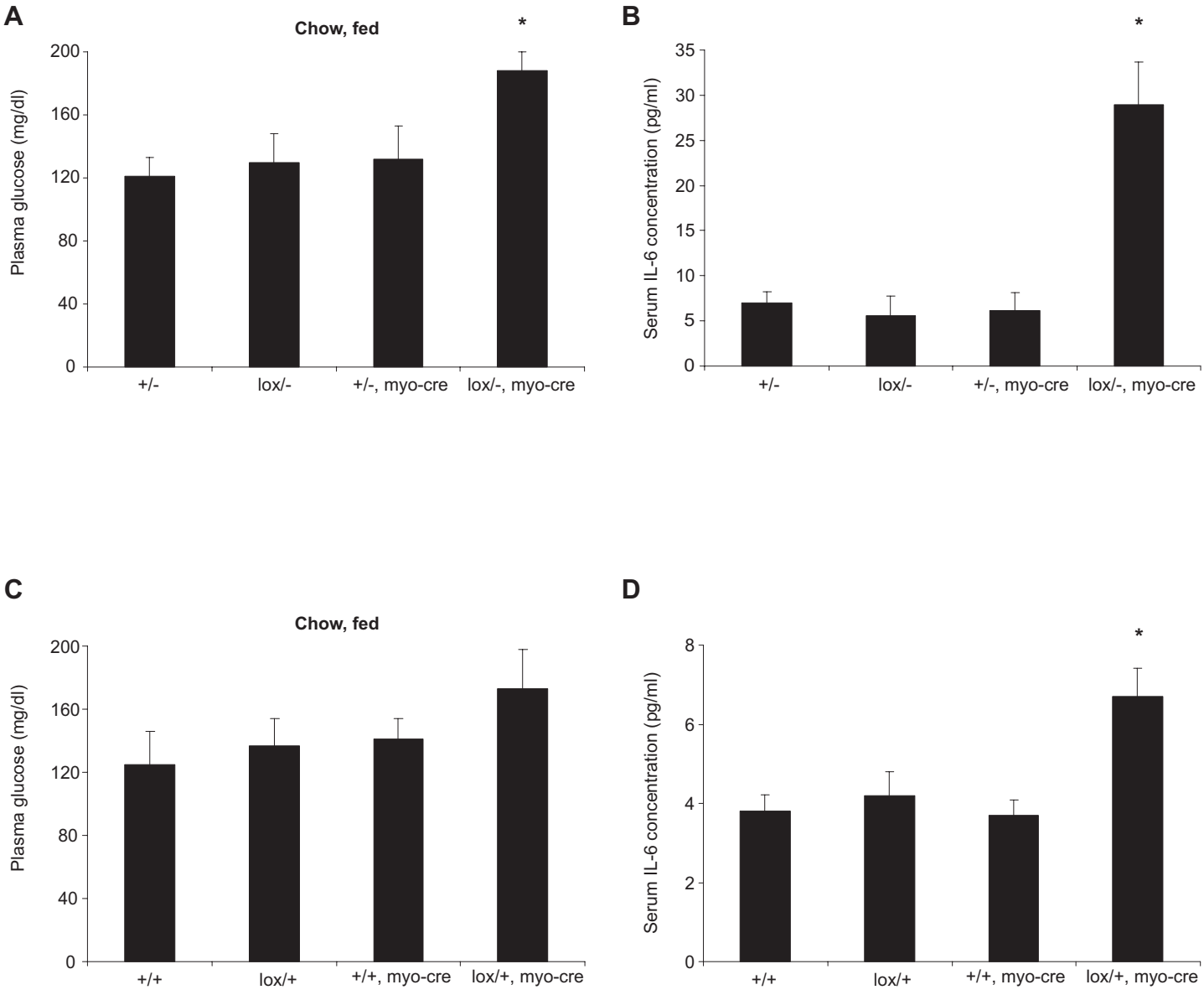

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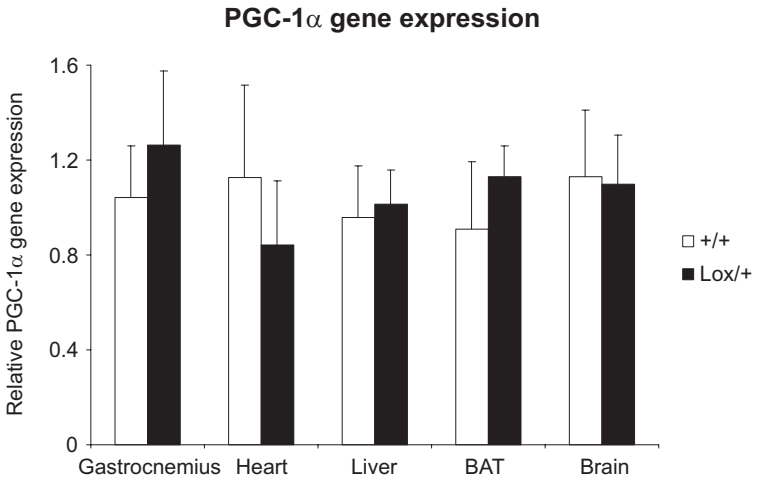

Supplemental Table T1

Multiple regression analysis for *IL-6* expression:

Independent variable	Regression coefficient	*P*-value
BMI	-1.29	0.112
Fasting glucose	2.89	0.694
Fasting insulin	0.68	0.857
PGC-1α (PPARGC1A)	-0.30	0.005

Multiple regression analysis for *TNFα* expression:

Independent variable	Regression coefficient	*P*-value
BMI	-0.97	0.375
Fasting glucose	2.92	0.771
Fasting insulin	-3.52	0.495
PGC-1α (PPARGC1A)	-0.35	0.016

Supplemental Table T2

	Control mice			PGC-1α muscle-specific knockout mice	Total
Genotype	+/-	Lox/-	+/-, myo-cre	Lox/-, myo-cre	
Number of animals (age 21 days, weaning)	20 (24.1%)	18 (21.7%)	22 (26.5%)	23 (27.7%)	83 (100%)

Supplemental Table T3

	Control mice			PGC-1α muscle-specific heterozygous mice	Total
Genotype	+/+	Lox/+	+/+, myo-cre	Lox/+, myo-cre	
Number of animals (age 21 days, weaning)	26 (26.8%)	26 (26.8%)	22 (22.7%)	23 (23.7%)	97 (100%)

Supplemental Fig. S1. Shift in substrate usage in MKOs. A, VCO_2 was determined by CLAMS with control and MKOs on a high fat diet. **B,** The respiratory exchange ratio was obtained from the VO_2 and VCO_2 values of control and MKOs. **C, D,** Serum non-esterified fatty acids (NEFA, panel C) and triglycerides (panel D) were determined from control and MKO mice. *$p<0.05$ between controls and MKOs.. n=8 per group.

Supplemental Fig. S2. Elevated uncoupling protein 1 (UCP-1) transcription in brown adipose tissue of MKOs. PGC-1α, PGC-1β, UCP-1 and diiodinase 2 (DIO2) mRNA levels were quantified in brown adipose tissue (BAT) by real-time PCR and normalized to 18S rRNA levels. *$p<0.05$ between control and MKOs. n=8 per group.

Supplemental Fig. S3. Altered insulin signaling in skeletal muscle of MKOs. A, Akt and IRS1-PI3K activities were quantified in skeletal muscle from control and MKOs fed a high fat diet for 3 weeks and exposed to hyperinsulinemic, euglycemic clamps. **B,** Akt and IRS2-PI3K activities were quantified in liver from control and MKOs fed a high fat diet for 3 weeks and exposed to hyperinsulinemic, euglycemic clamps. *$p<0.05$ between control and MKOs. Controls: n=7, MKOs: n=10 per group.

Supplemental Fig. S4. Normal expression of PGC-1α in islets of MKOs. A, Gene expression analysis of PGC-1α, PGC-1β and several PGC-1α target genes in isolated islets of control and MKOs. **B,** Transcript expression of cre recombinase in isolated islets, liver and gastrocnemius of cre positive mice. **C,** Analysis of genomic DNA from mouse tail, isolated islets and gastrocnemius of an MKO depicting absence of recombination in the islets. Bars depict mean values and error bars represent standard error. *p<0.05 between control and MKO animals. n=6 per group.

Supplemental Fig. S5. Control of inflammatory markers by PGC-1α in muscle cells. A, C2C12 myotubes were infected with adenoviral GFP and PGC-1α, respectively and harvested after 48 hours. RNA was isolated, relative gene expression measured by semiquantitative real-time PCR and normalized to 18S rRNA levels. *p<0.05 between GFP and PGC-1α-infected cells. **B, C,** Primary muscle cells obtained from control and global PGC-1α knockout mice were differentiated into myotubes and harvested after 6 days. RNA was isolated, relative gene expression measured by semiquantitative real-time PCR and normalized to 18S rRNA levels (panel B). Conditioned medium was harvested and IL-6 protein determined by ELISA (panel C). *p<0.05 between control and PGC-1α knockout cells. **D,** Areas covered by mononuclear infiltrates were quantified in H&E stained histological sections of gastrocnemius muscle from control and MKO animals.

Supplemental Fig. S6. Generation and analysis of PGC-1α muscle-specific heterozygous mice (SKM-Het). A, SKM-Het were generated by crossing mice with a floxed PGC-1α allele to animals that transgenically express cre recombinase under the control of the myogenin promoter and MEF2C enhancer (myo-cre). **B,** PGC-1α protein expression analysis in gastrocnemius of control, SKM-Het, whole body PGC-1α knockout animals (PGC-1α KO) and muscle-specific PGC-1α transgenic animals (MCK-PGC-1α). **C,** Relative expression of PGC-1α and PGC-1β mRNA was determined in different tissues obtained from control and SKM-Het animals. Bars depict mean values and error bars represent standard error. *p<0.05 between control and SKM-Het animals. n=8 per group.

Supplemental Fig. S7. Reduced ROS detoxification gene expression in SKM-Hets. ROS detoxifying gene expression was analyzed in gastrocnemius of control and SKM-Het animals by real-time PCR and normalized to 18S rRNA levels. Abbreviations: SOD, superoxide dismutase; Ant, adenine nucleotide translocator; Gpx, glutathione peroxidase; UCP, uncoupling protein. Bars depict mean values and error bars represent standard error. *p<0.05 between control and MKO animals. n=8 per group.

Supplemental Fig. S8. Increased circulating IL-6 levels in SKM-Hets, but not global heterozygous animals. A, Serum IL-6 concentration was determined from +/+, +/- and SKM-Het animals. **B,** Blood glucose levels are not significantly different between the different experimental groups. For this experiment, lox/+

females were crossed with +/-, myo-cre males and littermates were used for the analysis. *p<0.05 between the indicated groups. n=8 per group.

Supplemental Fig. S9. Unchanged metabolic parameters in SKM-Hets. A, B, C, Body weight (panel A), fat mass (panel B) and fat percentage (panel C) in 10 week old mice. **D,** Growth curve of control and SKM-Hets mice on a high fat diet. **E, F, G,** Food intake (panel E), heat production (panel F) and VO_2 per animal (panel G) were determined by using a comprehensive laboratory animal monitoring system (CLAMS) with control and SKM-Hets animals on a high fat diet. *p<0.05 between controls and SKM-Hets. n=6 per group.

Supplemental Fig. S10. No shift in substrate usage in SKM-Hets. A, VCO2 was determined by CLAMS with control and SKM-Hets on a high fat diet. **B,** The respiratory exchange ratio was obtained from the VO2 and VCO2 values of control and SKM-Hets. **C, D,** Serum non-esterified fatty acids (NEFA, panel C) and triglycerides (panel D) were determined from control and SKM-Het mice. *p<0.05 between controls and SKM-Hets. n=6 per group.

Supplemental Fig. S11. Elevated levels of SOCS3 and IL-6 in the pancreas of MKOs. RNA was isolated from pancreas, relative gene expression measured by semiquantitative real-time PCR and normalized to 18S rRNA levels. *p<0.05 between controls and MKOs. n=8 per group.

Supplemental Fig. S12. Blood glucose and IL-6 levels are not different between the three genotypically different control groups. A, C, Blood glucose was determined in fed mice on a regular chow diet. **B, D,** Serum IL-6 concentration was determined. n=6 per group, *p<0.05 between +/- and any of the other animals (panels A and B) or between +/+ and any of the other groups (panel C and D). n=8 per group.

Supplemental Fig. S13. No difference in PGC-1α mRNA expression in different tissues from wild type and lox/+ animals. Relative PGC-1α transcript levels in different tissues were determined by real-time PCR and normalized to 18S rRNA expression. n=6 per group.

Supplemental Table T1. Multiple regression analysis of IL-6 and TNFα expression in skeletal muscle of human volunteers. The expression of IL-6 and TNFα, respectively, was analyzed vs. the body mass index (BMI), fasting glucose levels, fasting insulin levels and PGC-1α (PPARGC1A) expression.

Supplemental Table T2. Genotypes of offspring from breeding to obtain PGC-1α muscle-specific knockout animals. Mice were genotyped at the age of 21 days (weaning).

Supplemental Table T3. Genotypes of offspring from breeding to obtain PGC-1α muscle-specific heterozygous animals. Mice were genotyped at the age of 21 days (weaning).