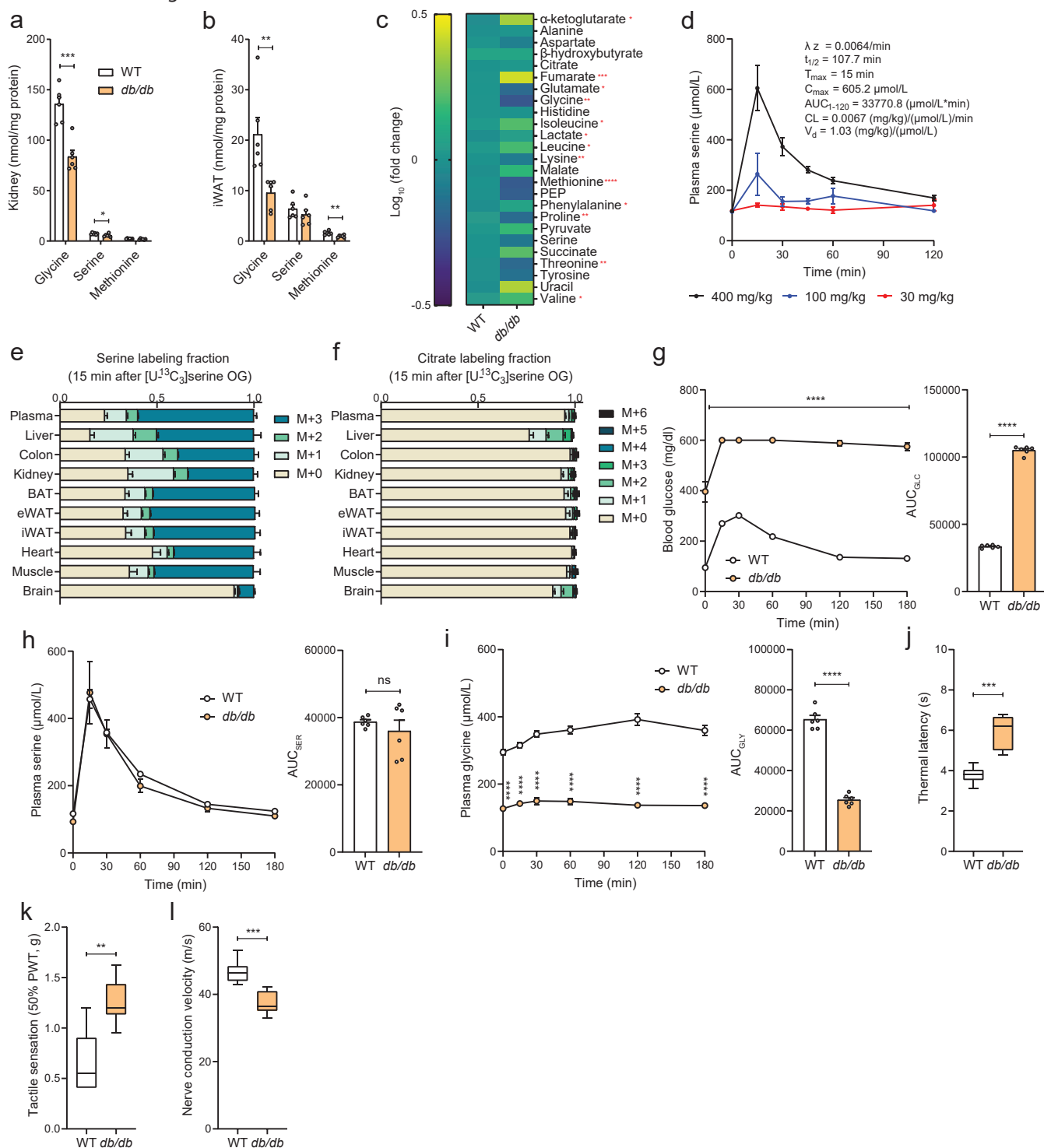


Extended Data Figure 1.

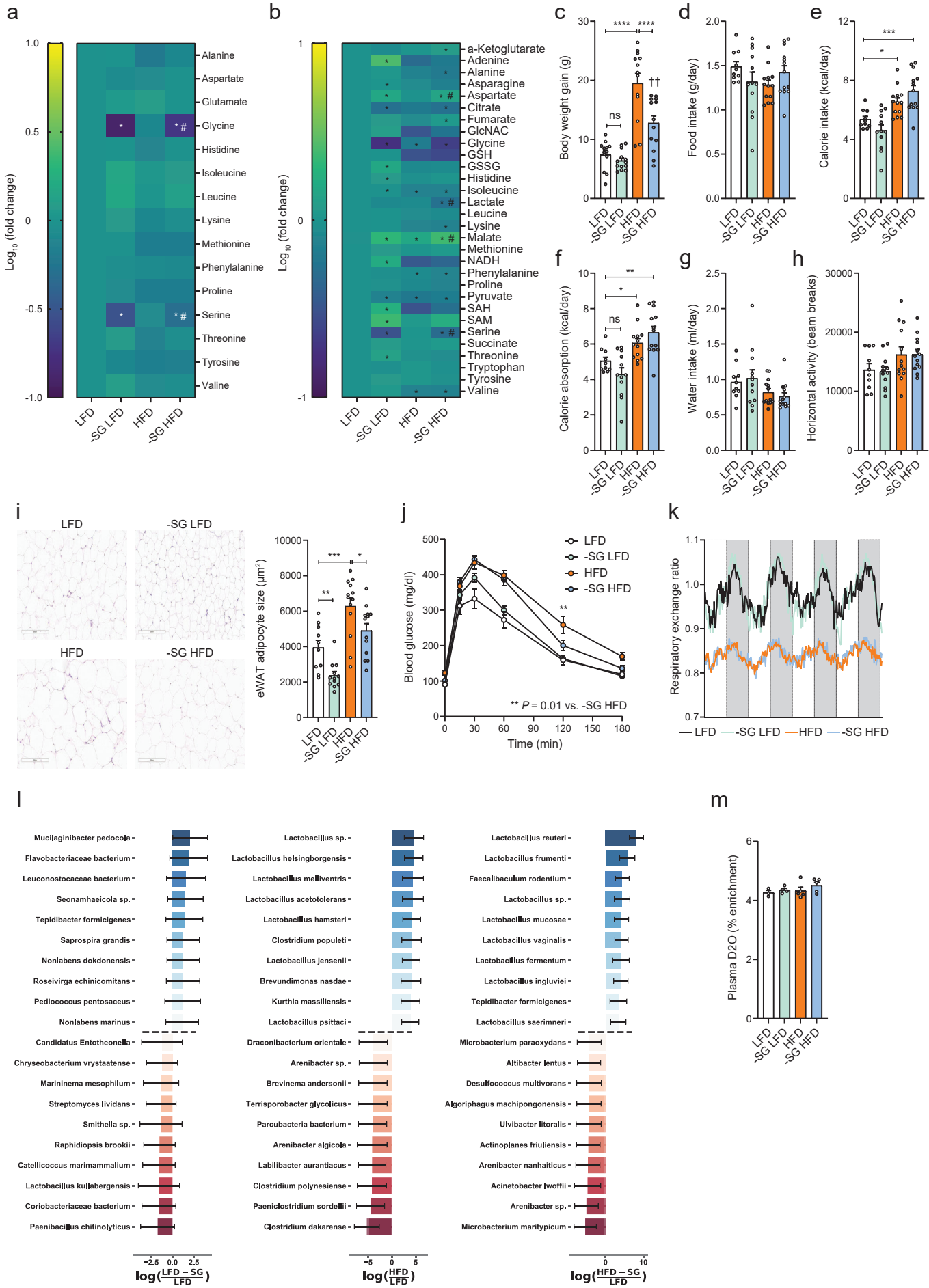


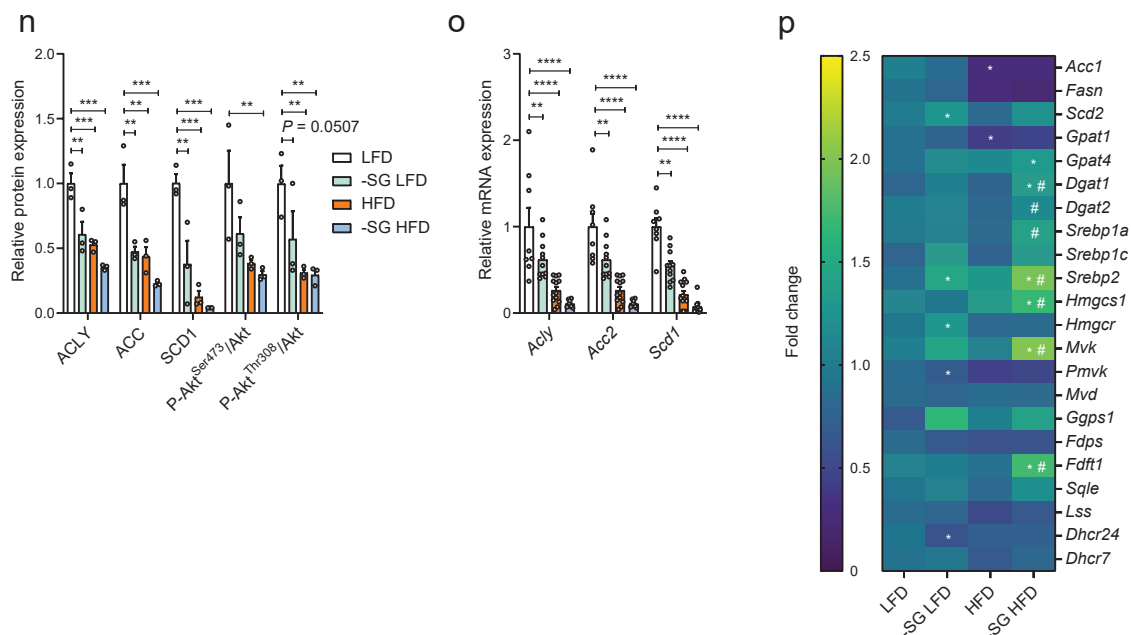
Extended Data Figure 1.

- (a) Levels of glycine, serine and methionine in WT and BKS-*db/db* mice in the kidney (n=6 per group).
 (b) Levels of glycine, serine and methionine in WT and BKS-*db/db* mice in the inguinal adipose tissue (iWAT) (n=6 per group).
 (c) Plasma metabolite levels in WT and BKS-*db/db* mice (n=6 per group).
 (d) Serine tolerance test (STT) in WT mice (n=4 group dosage).
 (e) Tissue serine labeling fraction in WT mice 15 minutes after [U-¹³C]₃serine administration via oral gavage (n=4 per tissues).
 (f) Tissue citrate labeling fraction in WT mice 15 minutes after [U-¹³C]₃serine administration via oral gavage (n=4 per tissues).
 (g) Plasma glucose pharmacokinetics and area under curve in WT and BKS-*db/db* mice following OGTT with glucose dosed at 2 g/kg (n=6 per group).
 (h) Plasma serine pharmacokinetics and area under curve in WT and BKS-*db/db* mice following STT with serine dosed per body weight (400 mg/kg) (n=6 per group).
 (i) Plasma glycine pharmacokinetics and area under curve in WT and BKS-*db/db* mice following GTT/STT with serine dosed per body weight (n=6 per group).
 (j) Thermal latency in WT and BKS-*db/db* mice (n=6 per group).
 (k) Tactile sensation in WT and BKS-*db/db* mice (n=6 per group).
 (l) Nerve conduction velocity in WT and BKS-*db/db* mice (n=6 per group).

Data are mean ± standard error of mean (SEM) and were analyzed using independent t-test (a-c, g-l) and two-way ANOVA with Fisher's LSD post hoc test (g-i). * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001.

Extended Data Figure 2.



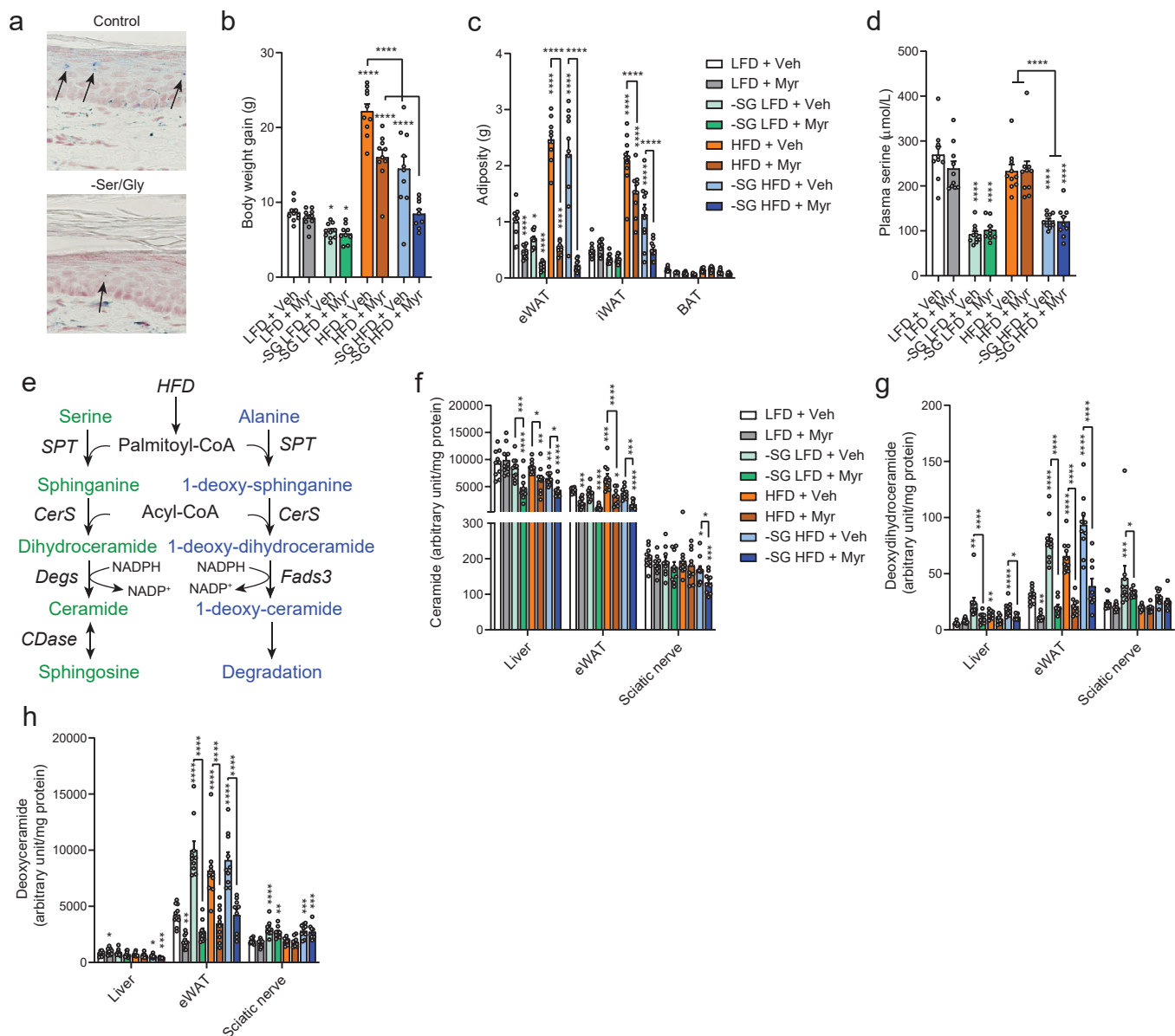


Extended Data Figure 2.

- (a) Plasma amino acid heatmap in mice fed low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=5-8 per group).
- (b) Liver metabolite content in mice fed serine/glycine replete and deplete LFD and HFD diet (n=9-10).
- (c) Body weight gain 18 weeks after dietary intervention (n=13 per group).
- (d) Food intake in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (e) Calorie intake in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (f) Calorie absorption in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (g) Water intake in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (h) Physical activity in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (i) Representative images and quantification of adipocyte size in response to dietary feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (j) I.P. glucose tolerance test 18 weeks after feeding with a low fat diet (LFD) or high fat diet (HFD) replete or deficient in serine and glycine (n=10-13 per group).
- (k) Respiratory exchange ratio time course (n=10-13 per group).
- (l) Log fold change of microbiome species (n=9-10 per group).
- (m) Plasma heavy water (D₂O) enrichment (n=3-5 mice per group).
- (n) Hepatic protein expression of ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and steroyl-CoA desaturase 1 (SCD1), P-AktS473, and P-AktT308 (n=3 per group).
- (o) Hepatic mRNA expression of ATP-citrate lyase (Acly), acetyl-CoA carboxylase (Acc2), and steroyl-CoA desaturase 1 (Scd1) (n=8-13 per group).
- (p) Hepatic mRNA expression of enzymes involved in fatty acid and cholesterol synthesis (n=8-13 per group).

Data are mean $\pm$ standard error of mean (SEM) and were analyzed using two-way ANOVA with Fisher's LSD post hoc test (a-j, m-p). * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001 vs. LFD unless otherwise indicated. †† P < 0.01 vs. LFD. # P < 0.05 vs. LFD.

Extended Data Figure 3.



Extended Data Figure 3.

(a) Representative images of intraepidermal nerve fiber (IENF) density in mice fed control or serine/glycine free diet. PGP9.5 staining of IENF is shown by arrows.

(b) Body weight gain 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

(c) Adipose tissue size 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

(d) Plasma serine concentration 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

(e) Schematic of serine palmitoyltransferase (SPT) promiscuity and de novo sphingolipid biosynthesis pathway

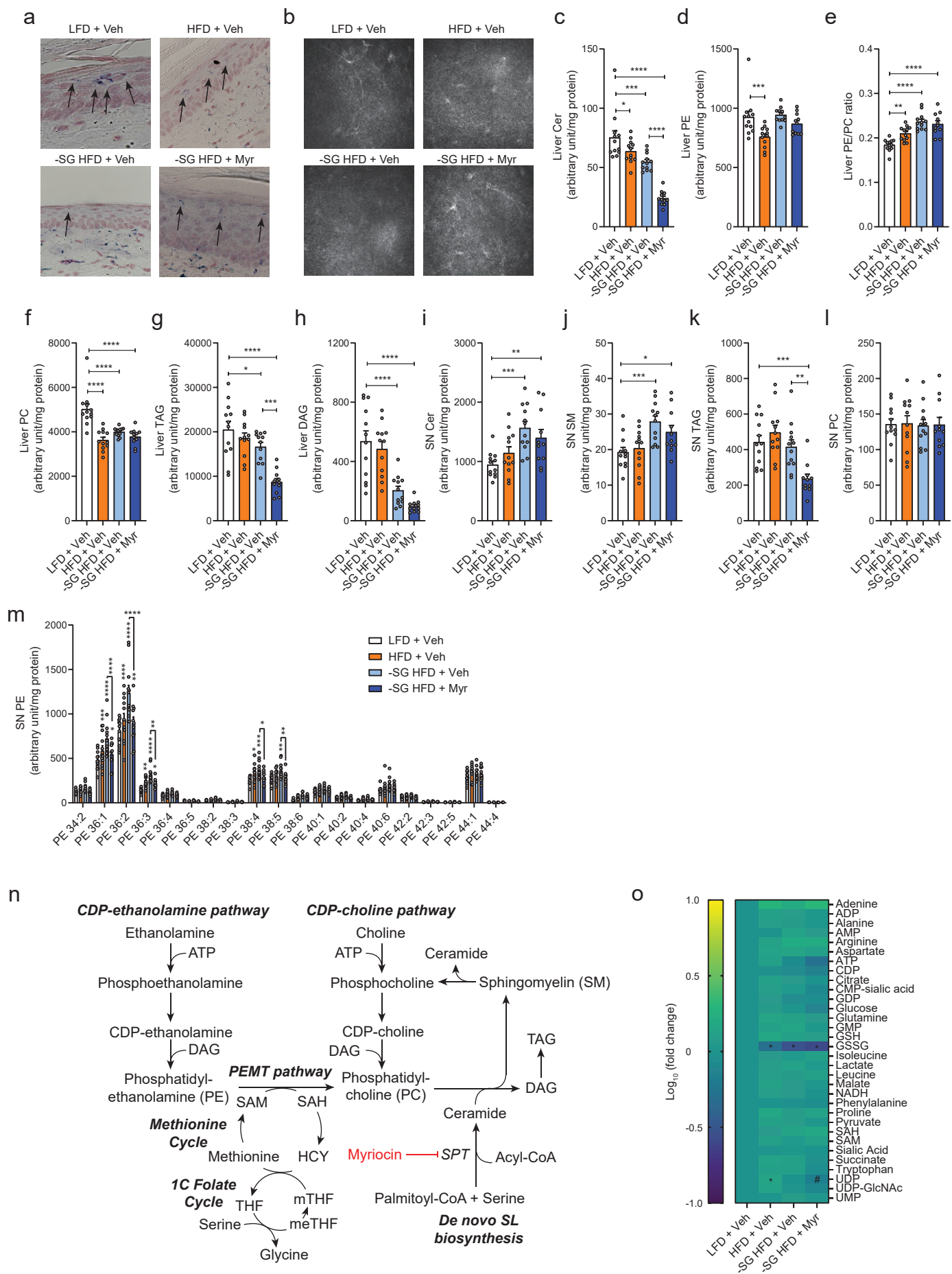
(f) Liver, epididymal adipose tissue (eWAT), and sciatic nerve ceramide content 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

(g) Liver, epididymal adipose tissue (eWAT), and sciatic nerve deoxydihydroceramide content 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

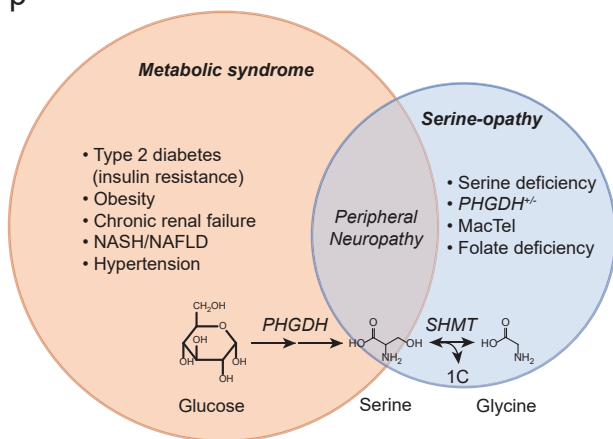
(h) Liver, epididymal adipose tissue (eWAT), and sciatic nerve deoxyceramide content 6 months after dietary intervention and myriocin treatment (n=9-10 per group).

Data are mean $\pm$ standard error of mean (SEM) and were analyzed using one-way ANOVA with Fisher's LSD post hoc test (b-d, f-h). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ vs. LFD + Veh group unless otherwise indicated.

Extended Data Figure 4.



p



Extended Data Figure 4.

- Representative images of intraepidermal nerve fiber (IENF) density in mice treated with vehicle or myriocin during dietary interventions. PGP9.5 staining of IENF is shown by arrows.
- Representative images of corneal nerves in mice treated with vehicle or myriocin during dietary interventions.
- Hepatic ceramide (Cer) content (n=11-12 per group).
- Hepatic phosphatidylethanolamine (PE) content (n=11-12 per group).
- Hepatic phosphatidylethanolamine (PE)/phosphatidylcholine (PC) ratio (n=11-12 per group).
- Hepatic phosphatidylcholine (PC) content (n=11-12 per group).
- Hepatic triacylglyceride (TAG) content (n=11-12 per group).
- Hepatic diacylglyceride (DAG) content (n=11-12 per group).
- Sciatic nerve ceramide (Cer) content (n=11-12 per group).
- Sciatic nerve sphingomyelin (SM) content (n=11-12 per group).
- Sciatic nerve triacylglyceride (TAG) content (n=11-12 per group).
- Sciatic nerve phosphatidylcholine (PC) content (n=11-12 per group).
- Sciatic nerve distribution of phosphatidylethanolamine (PE) species (n=11-12 per group).
- Metabolic map linking serine/glycine metabolism with complex lipids.
- Sciatic nerve polar metabolite heatmap (n=11-12 per group).
- Schematic illustrating impacts of metabolic syndrome and serine-opathy on serine metabolism and peripheral neuropathy.

Data are mean $\pm$ standard error of mean (SEM) and were analyzed using one-way ANOVA with Fisher's LSD post hoc test (c-l, o), and two-way ANOVA with Fisher's LSD post hoc test (m).

* P < 0.05, ** P < 0.01, *** P < 0.001 vs. LFD + Veh group unless otherwise indicated. # P < 0.05 vs. LFD + Veh.