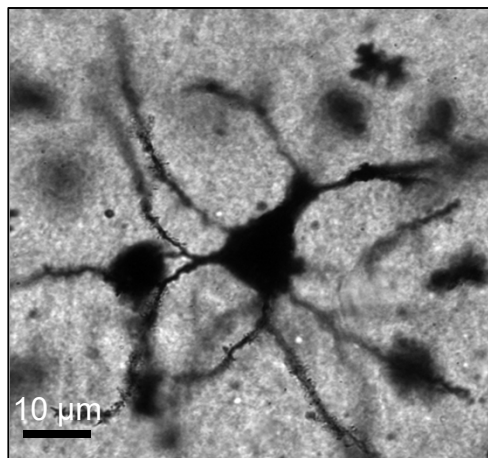
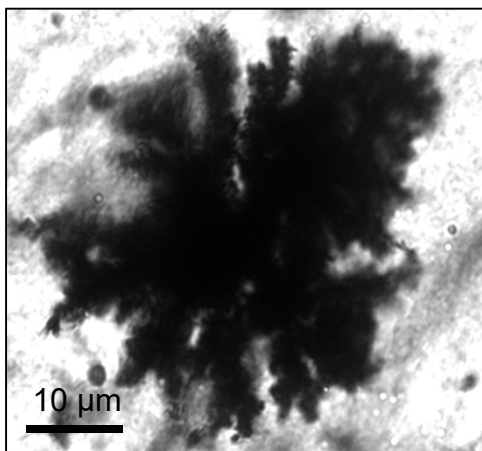


Figure S1

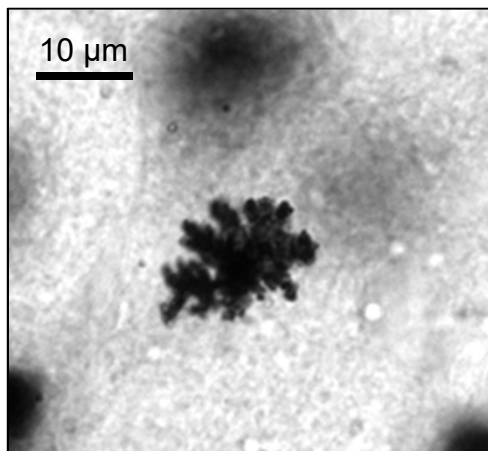
Neuron



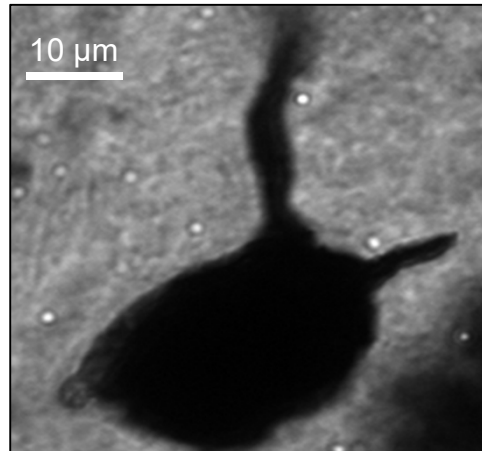
Astrocyte



Microglia

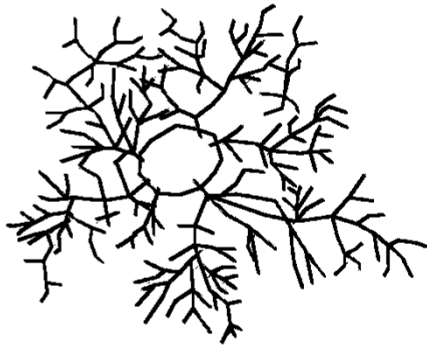


Oligodendrocyte



**A**

ARC – Ad-lib feeding



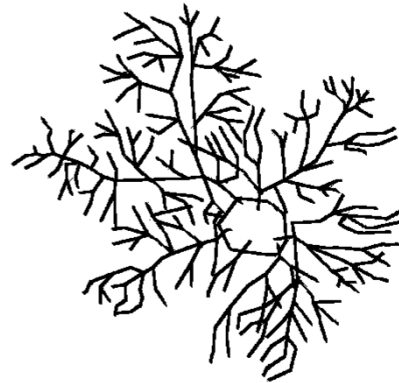
ARC – Fasting



VMH – Ad-lib feeding



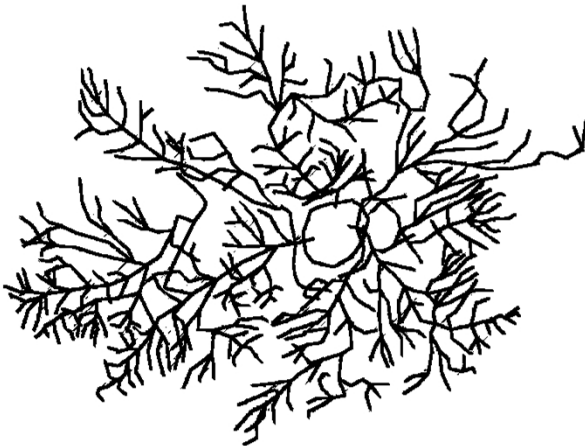
VMH – Fasting



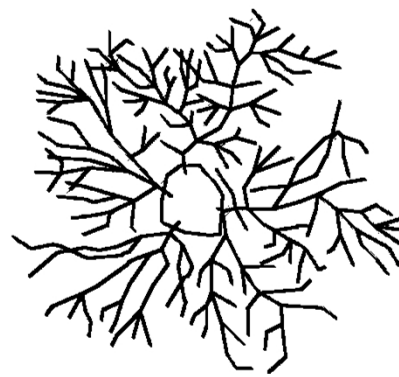
3-month-old male C57BL/6

**B**

VMH – Ad-lib chow



VMH – Ad lib HFD



5-month-old male C57BL/6

Figure S3

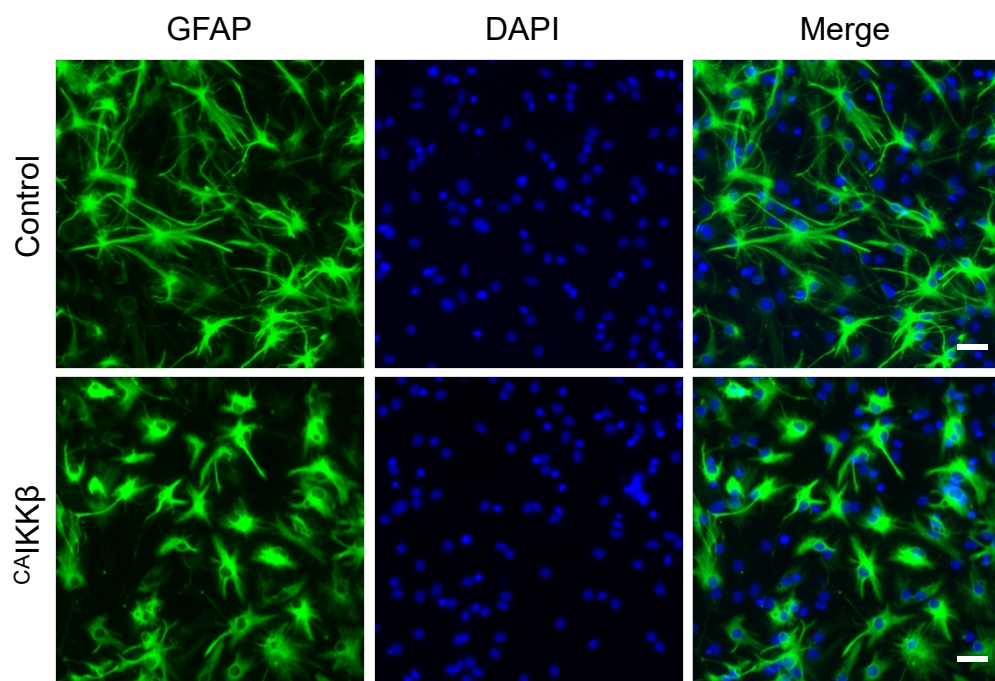


Figure S4

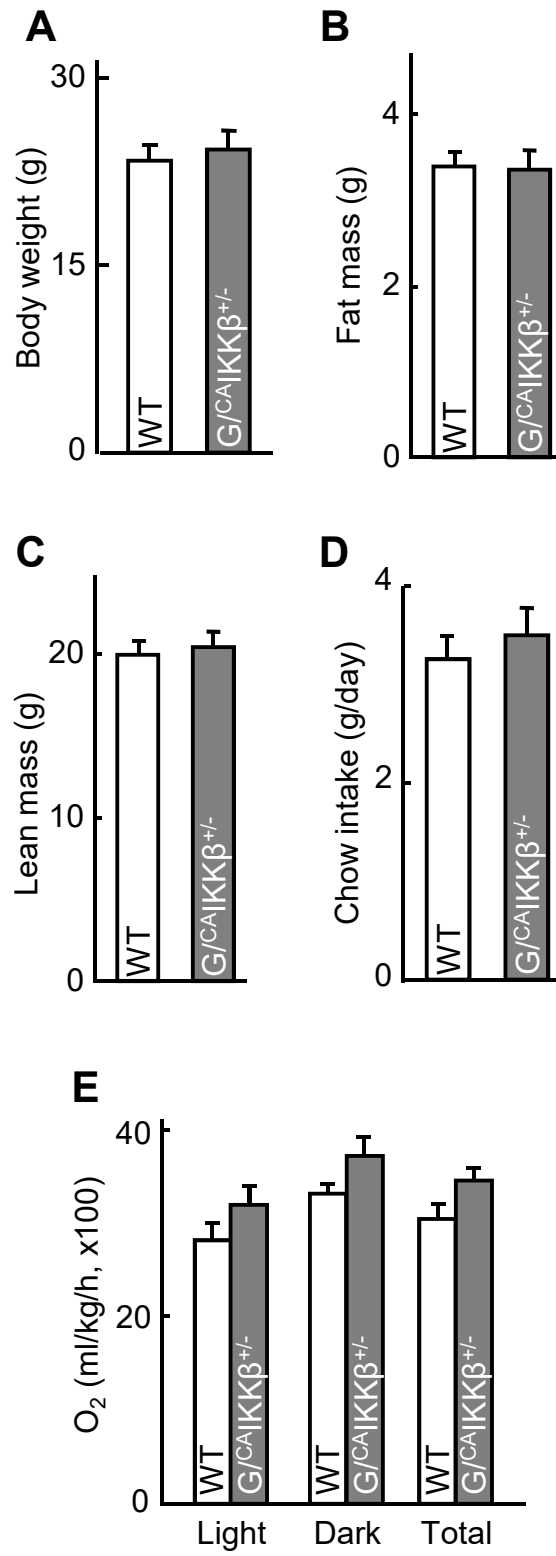


Figure S5

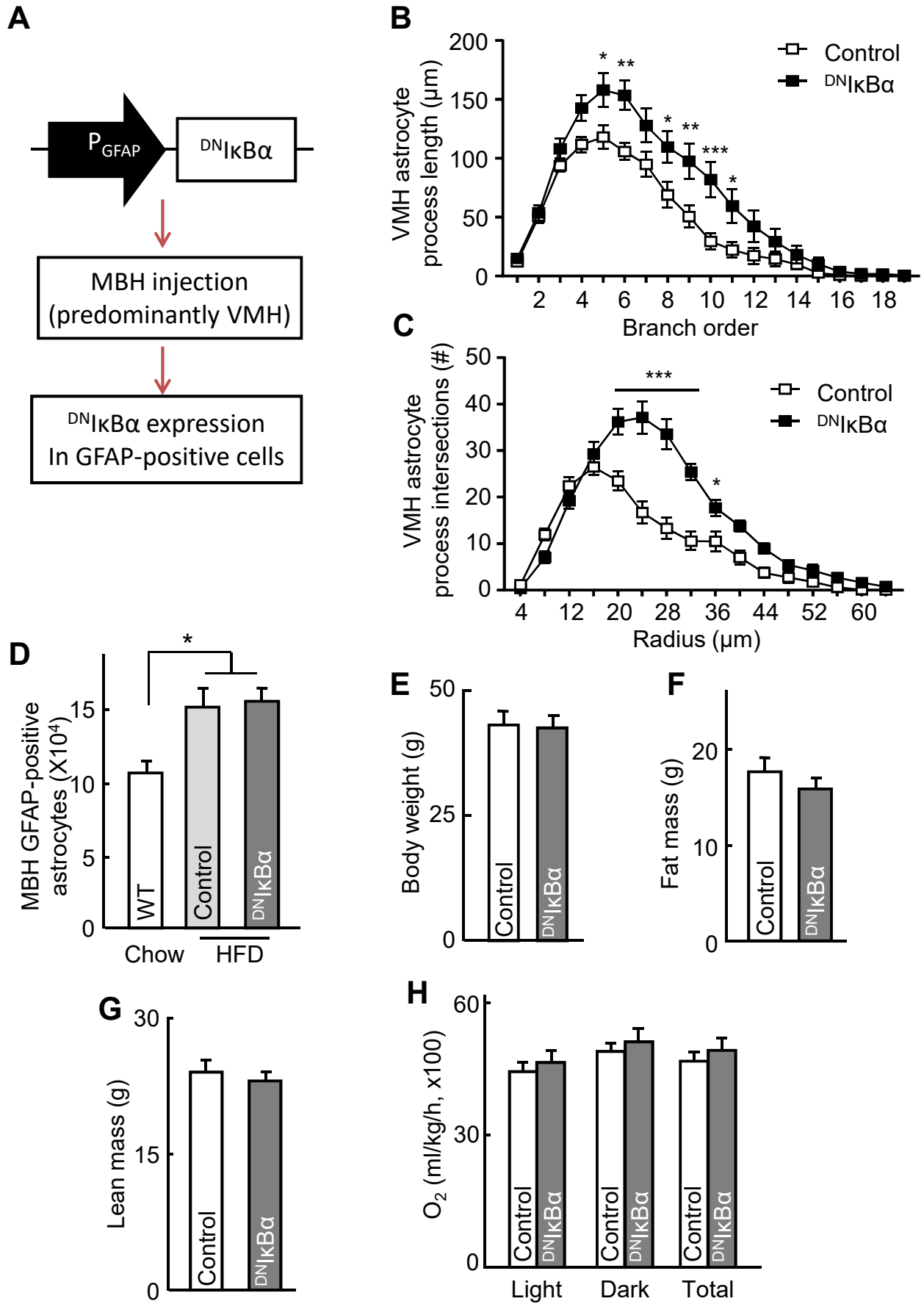
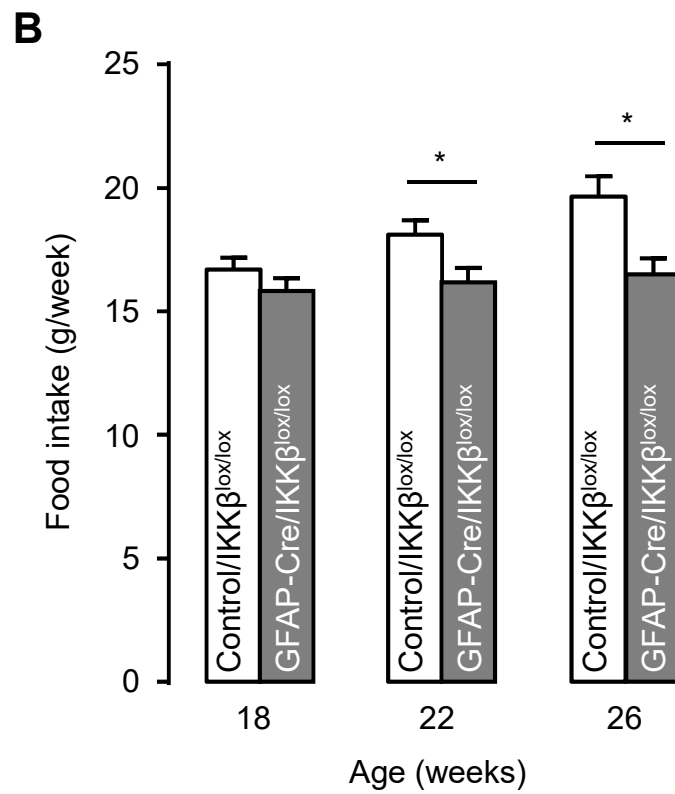
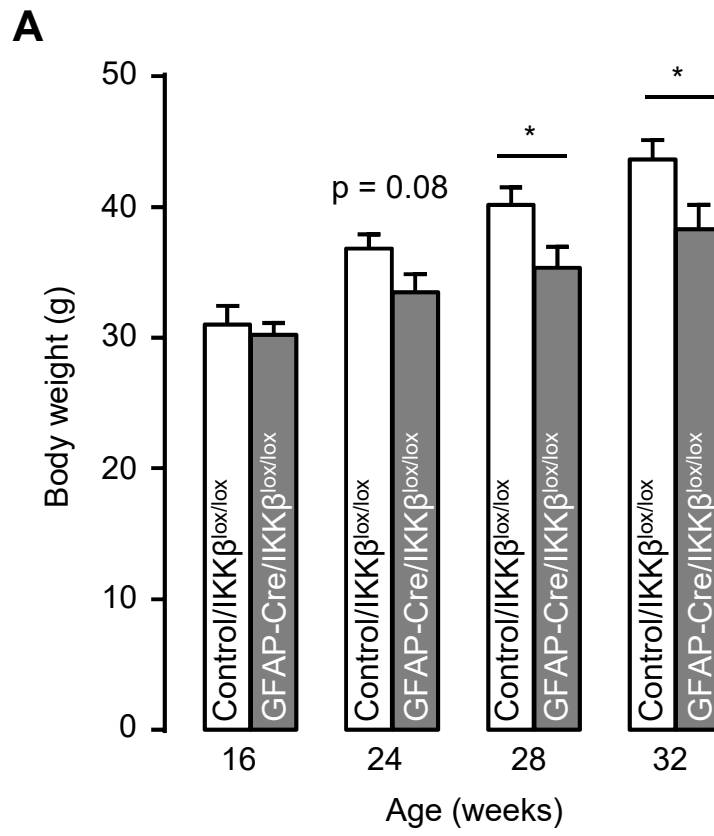
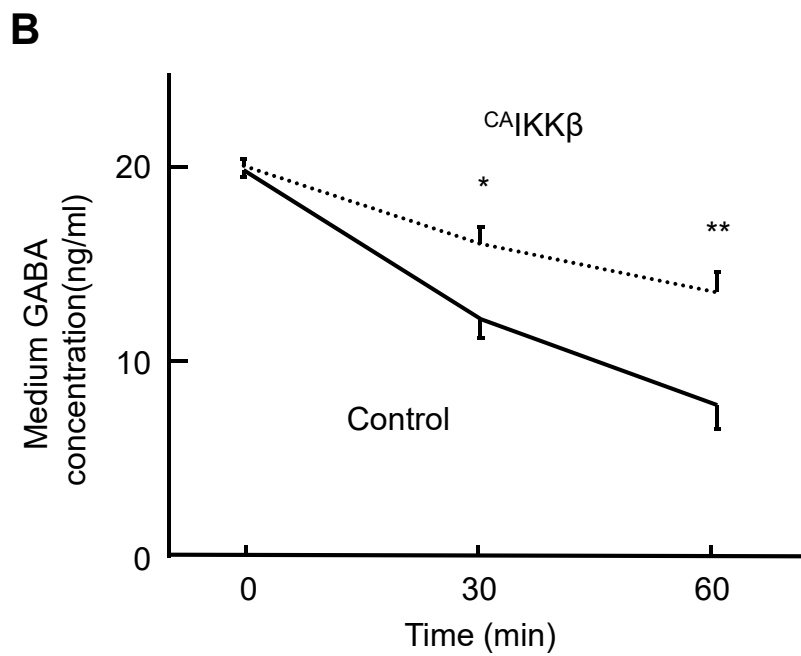
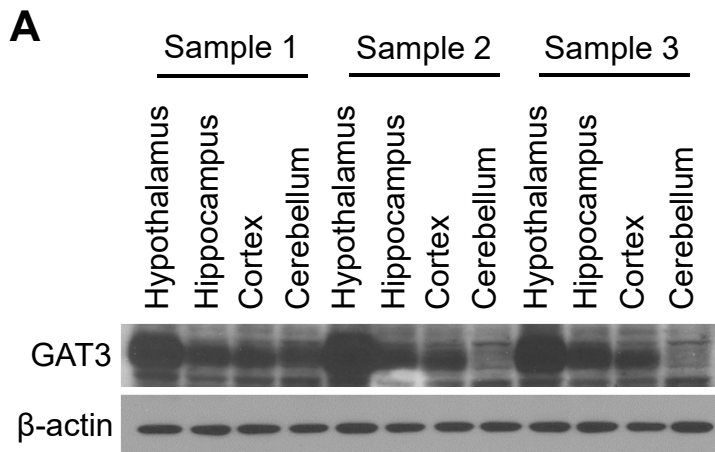


Figure S6





## Supplemental Figure Legends

**Figure S1. Representative Golgi staining images of different neural cells, related to Figure 1–3.** Representative images of Golgi staining are presented to demonstrate different morphologies of neurons, astrocytes, microglia and oligodendrocytes. Scale bar, 10  $\mu\text{m}$ .

**Figure S2. Representative astrocytic process tracing, related to Figure 1–2.** Computerized tracing of representative astrocytes and processes from Golgi staining for the experiments in Figure 1 (A) and Figure 2A–B (B). Scale bar, 10  $\mu\text{m}$ .

**Figure S3. Effect of IKK $\beta$ /NF- $\kappa$ B over-activation on plasticity of cultured astrocytes, related to Figure 2.** Astrocytes were isolated from new-born C57BL/6 mice and infected with  $^{CA}$ IKK $\beta$  expressing or control lentivirus and immunostained for GFAP. Scale bar, 20  $\mu\text{m}$ .

**Figure S4. Additional physiological profiles of GFAP/ $^{CA}$ IKK $\beta^{+/-}$  mice, related to Figure 3 and 4.** Chow-fed GFAP/ $^{CA}$ IKK $\beta^{+/-}$  mice vs. littermate genotype-matched (lox-STOP-lox- $^{CA}$ IKK $\beta^{+/-}$ ) WT mice (3~4-month-old males) were measured for body weight (A), fat mass (B), lean mass (C), daily food intake (D) and O<sub>2</sub> consumption (normalized by lean mass) (E). n = 9–10 mice per group (A–E). Error bars reflect mean  $\pm$  s.e.m.

**Figure S5. HFD-fed mice with astrocytic NF- $\kappa$ B inhibition, related to Figure 3.** GFAP promoter-driven  $^{DN}$ I $\kappa$ B $\alpha$  vs. control lentiviruses (both containing GFP) were injected bilaterally into the MBH of 5-month-HFD-fed male C57BL/6 mice as elucidated in (A); at 1–2 weeks post viral injection, mice were studied for histology including (B, C) Golgi staining followed by



tracing of astrocytes and processes and **(D)** immunostaining of GFAP followed by counting of GFAP-positive cells in the MBH (which were also compared to samples from age-matched chow fed mice), and studied for physiology including measurements of **(E–H)** body weight **(E)**, lean mass **(F)**, fat mass **(G)** and O<sub>2</sub> consumption (normalized by lean mass) **(H)**. Scale bar, 100 μm.\*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; n = 15 data sets from 5 mice per group, compared between lentiviral GFAP/<sup>DN</sup>IκBα injected mice and control virus injected mice at indicated points **(B, C)**; n = 4 mice per group **(D)**; n = 9 – 10 mice per group **(E–H)**. Error bars reflect mean ± s.e.m.

**Figure S6. HFD-fed mice with MBH astrocytic NF-κB inhibition, related to Figure 4.** Adult IKKβ<sup>lox/lox</sup> mice (chow-fed males, ~14 weeks old) received bilateral MBH injections of GFAP promoter-driven Cre vs. control lentiviruses and subsequently were maintained on a HFD and followed up for body weight **(A)** and HFD intake **(B)**. \*  $p < 0.05$ ; n = 7–8 mice per group, Error bars reflect mean ± s.e.m.

**Figure S7. GAT3 expression and GABA uptake, related to Figure 5–7.** Tissues of the hypothalamus, hippocampus, cortex and cerebellum from adult chow-fed male C57BL/6 mice were collected and analyzed for GAT3 protein levels via western blotting **(A)**. Astrocytes were isolated from new-born C57BL/6 mice, cultured and infected with <sup>CA</sup>IKKβ expressing or control lentivirus, subsequently 20 ng/ml GABA were added into culture medium at minute 0, and GABA in the medium were measured at indicated time points **(B)**. \*  $p < 0.05$ , \*\*  $p < 0.01$ , n = 3 samples per group per point. Error bars reflect mean ± s.e.m.