**Supplemental Figure 1. Related to Figure 1**

(**A**-**C**) Volcano plots of gene expressions in the brain. Red (upregulated genes) and blue (downregulated genes) dots represent genes with a p-value less than 0.02. (**D**) GSEA (MSigDB) analysis in the brain (KD [12 months] vs CD [12 months]). (**E**) Protein expressions of brains (CD [12 months] and KD [12 months]) (n = 6 per group).

**Supplemental Figure 2. Related to Figure 1**

(**A**) GSEA (MSigDB) analysis in the brain (CD [26 months] vs CD [12 months]). (**B**)Heatmap of gene expressions in the brain. (**C**) Heatmap of gene expression (analyzed by qPCR) of brains harvested at 12 or 22 months old (12-month-old or 22-month-old maintained on CD or KD for one week). P-values (KD [22 months] vs CD [22 months]) are calculated by unpaired two-tailed t test.

**Supplemental Figure 3. Related to Figure 1**

(**A**-**C**) GSEA (GO) analysis in the brain. (**D**-**F**) GSEA (KEGG) analysis in the brain.

**Supplemental Figure 4. Related to Figure 1**

(**A**) Deconvolution of gene expression in the brain by the CIBERSORTx analysis.

**Supplemental Figure 5. Related to Figure 1**

(**A**) Experimental timeline. An RNA-seq analysis of livers (KD [12 months] vs CD [12 months]) was published previously15. (**B**) Volcano plot of gene expressions in the liver (Cyclic KD [26 months] vs CD [26 months]). Red (upregulated genes) and blue (downregulated genes) dots represent genes with a p-value less than 0.02. (**C**) GSEA (MSigDB) analysis in the liver (Cyclic KD [26 months] vs CD [26 months]). (**D**)Heatmap of gene expressions in the liver (CD [26 months] and Cyclic KD [26 months]).

**Supplemental Figure 6. Related to Figure 1**

(**A**) GSEA (GO) analysis in the liver (Cyclic KD [26 months] vs CD [26 months]). (**B**) GSEA (KEGG) analysis in the liver (Cyclic KD [26 months] vs CD [26 months]). (**C**) Heatmap of gene expression in the liver (CD [12 months] and KD [12 months]).

**Supplemental Figure 7. Related to Figure 1**

(**A**) Body weight and liver weight of individual mice. (**B**) Volcano plots of Pearson correlation between liver weight and liver gene expression (CD [26 months] and Cyclic KD [26 months]). Red (positively correlated genes) and blue (negatively correlated genes) dots represent genes with a p-value less than 0.02. (**C**) GSEA (MSigDB) analysis of Pearson correlation between liver weight and liver gene expression (CD [26 months] and Cyclic KD [26 months]). (**D**) Simple linear regression between liver weight and liver gene expression (CD [26 months] and Cyclic KD [26 months]). R2: R squared. \**p* < 0.05.

**Supplemental Figure 8. Related to Figure 1**

(**A**) RRHO analysis comparing Cyclic KD in the brain (pink) with the liver (brown). (**B**) Volcano plots of Pearson correlation between liver gene expression and brain gene expression (CD [26 months] and Cyclic KD [26 months]). Red (positively correlated genes) and blue (negatively correlated genes) dots represent genes with a p-value less than 0.02. (**C**) GSEA (MSigDB) analysis of Pearson correlation between liver gene expression and brain gene expression (CD [26 months] and Cyclic KD [26 months]). (**D**) Simple linear regression between liver gene expression and brain gene expression (CD [26 months] and Cyclic KD [26 months]). R2: R squared. \**p* < 0.05. (**E**) Simple linear regression between liver gene expression and brain gene expression (CD [12 months] and KD [12 months]). R2: R squared. \**p* < 0.05.

**Supplemental Figure 9. Related to Figure 1**

(**A**) Volcano plots of Pearson correlation between liver weight and brain gene expression (CD [26 months] and Cyclic KD [26 months]). Red (positively correlated genes) and blue (negatively correlated genes) dots represent genes with a p-value less than 0.02. (**B**) GSEA (MSigDB) analysis of Pearson correlation between liver weight and brain gene expression (CD [26 months] and Cyclic KD [26 months]). (**C**) Simple linear regression between liver weight and brain gene expression (CD [26 months] and Cyclic KD [26 months]). R2: R squared. \**p* < 0.05.

**Supplemental Figure 10. Related to Figure 1**

(**A**) Experimental timeline with mouse numbers. (**B**) CD4+ cells, CD8+ cells, and CD8+/CD4+ ratio in the blood. (**C**) Foxp3+ cells in the blood. (**D**) PD-1+/CD4+ and PD-1+/CD8+ cells in the blood. All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons.

**Supplemental Figure 11. Related to Figure 2**

(**A**) mRNA expression in human primary microglia (n = 2 per each group). All data are presented as mean ± SD. (**B**-**D**) Volcano plots of gene expressions in human primary neurons (**B**), human primary astrocytes (**C**), and human primary microglia (**D**). Red (upregulated genes) and blue (downregulated genes) dots represent genes with a p-value less than 0.02.

**Supplemental Figure 12. Related to Figure 2**

(**A**) GSEA (MSigDB) analysis in human primary neurons, astrocytes, and microglia (+ LPS vs − LPS). (**B**) Heatmap of “G2-M Checkpoint” genes. (**C**) Heatmap of “TNFα Signaling via NFκB” genes. (**D**) Heatmap of “Inflammatory Response” genes. (**E**) Heatmap of “Interferon Gamma Response” genes. (**F**) Heatmap of genes related to ketone metabolism and monocarboxylate transporters (MCTs).

**Supplemental Figure 13. Related to Figure 2**

(**A**-**C**) GSEA (GO) analysis in human primary neurons (**A**), astrocytes (**B**), and microglia (**C**).

**Supplemental Figure 14. Related to Figure 2**

(**A**-**C**) GSEA (KEGG) analysis in human primary neurons (**A**), astrocytes (**B**), and microglia (**C**).

**Supplemental Figure 15. Related to Figure 2**

(**A**) RRHO analysis comparing R-BHB without LPS (R-BHB [– LPS] vs Ctrl [– LPS]) in brain cells with one week KD (KD [12 months]) vs CD [12 months]) in the brain. (**B**) RRHO analysis comparing LPS (Ctrl [+ LPS] vs Ctrl [– LPS]) in brain cells with aging (CD [26 months] vs CD [12 months]) in the brain. (**C**) RRHO analysis comparing R-BHB with LPS (R-BHB [+ LPS] vs Ctrl [+ LPS]) in brain cells with Cyclic KD (Cyclic KD [26 months] vs CD [26 months]) in the brain.

**Supplemental Figure 16. Related to Figure 3**

(**A**) Compound structures and the pH in the compounds' culture medium. (**B**-**D**) mRNA expression in mouse primary microglia (n = 3-4 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. (**B**) Compare the mean of each sample with the mean of “0 mM”. (**C**) Compare the mean of each sample with the mean of “Ctrl → LPS”. (**D**) Compare the mean of each sample with the mean of “Ctrl + LPS”. (**E**) Seahorse mito stress assay in mouse primary microglia (n = 13-15 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. All data are representative of two independent experiments. Abbreviation: FCCP, carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone.

**Supplemental Figure 17. Related to Figure 3**

(**A**) mRNA expression in mouse primary microglia (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. All data are representative of two independent experiments.

**Supplemental Figure 18. Related to Figure 3**

(**A**) Experimental timeline. (**B**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse primary microglia (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP” or “Ctrl + nigericin”. (**C**) Western blot analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse primary microglia (n = 1-2 per group). (**D**-**E**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse primary microglia (n = 2-3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP” (**D**) or “Ctrl + nigericin” (**E**). All data are representative of two independent experiments.

**Supplemental Figure 19. Related to Figure 3**

(**A**-**C**) mRNA expression in mouse primary microglia (n = 3-4 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. All data are representative of two independent experiments.

**Supplemental Figure 20. Related to Figure 3**

(**A**) mRNA expression in mouse primary astrocytes (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl”. (**B**) Protein expression in mouse primary astrocytes (n = 2 per group). All data are representative of two independent experiments.

**Supplemental Figure 21. Related to Figure 3**

(**A**) mRNA expression in mouse IMG microglia cells (n = 2 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl”. (**B**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse IMG cells (n = 3 per group). One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP” or “Ctrl + nigericin”. (**C**) Protein expression in mouse IMG cells (n = 2 per group). All data are representative of two independent experiments.

**Supplemental Figure 22. Related to Figure 3**

(**A**) mRNA expression in mouse BV-2 microglia cells (n = 2 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl”. (**B**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse BV-2 cells (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP” or “Ctrl + nigericin”. (**C**) Protein expression in mouse BV-2 cells (n = 2 per group). All data are representative of two independent experiments.

**Supplemental Figure 23. Related to Figure 3**

(**A**) mRNA expression in mouse bone marrow-derived macrophages (BMDMs) (n = 2 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of Ctrl. (**B**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse BMDMs (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP” or “Ctrl + nigericin”. (**C**) Protein expression in mouse BMDMs (n = 2 per group). All data are representative of two independent experiments.

**Supplemental Figure 24. Related to Figure 4**

(**A**) mRNA expression in mouse primary microglia (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + LPS”. All data are representative of two independent experiments. (**B**) ELISA analysis of IL-1β secretion after NLRP3 inflammasome activation in mouse primary microglia (n = 3 per group). All data are presented as mean ± SD. One-way ANOVA with Dunnet’s correction for multiple comparisons. Compare the mean of each sample with the mean of “Ctrl + ATP”. All data are representative of two independent experiments.

**Supplemental Data 1. Related to Figure 1**

Information on GSEA (MSigDB) analysis in the brain (KD [12 months] vs CD [12 months], CD [26 months] vs CD [26 months], and Cyclic KD [26 months] vs CD [26 months]) and the liver (Cyclic KD [26 months] vs CD [26 months]).

**Supplemental Data 2. Related to Figure 2**

Information on GSEA (MSigDB) analysis in human primary neurons, astrocytes, and microglia.