SUPPLEMENTAL ITEMS:

FigureS1. Mgll protein levels in 3xTg-AD and *Cbp*S436A mice hippocampal DG and human post-mortem AD hippocampal DG tissues.

Figure S2. JZL 184 and metformin do not significantly change general motor activities of WT and *Cbp*S436A, and Non-Tg and 3xTg-AD mice.

Figure S3. Metformin treatment removes intracellular β-amyloid accumulation from 3xTg hippocampal dentate gyrus.

Figure S4. (A) ChIP-qPCR analysis for CBP binding at Mgll promoter in differentiating

WT and CbpS436A NPCs in the presence of metformin; (B-D) Efficiency of shRNA-

mediated Mgll knockdown.

Figure S5. Continued passaging does not change total aPKC protein levels.

Figure S6. AMPK protein expression in 3xTg-AD and Non-Tg NPCs.

 Table S1. Human post-mortem samples information regarding age, sex and post-mortem

 delay.

Table S2. **RNA-seq analysis of differentiating WT and** *Cbp***S436A NPCs in the presence of metformin.**

Supplementary Materials:



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Figure S1. Mgll protein levels in 3xTg-AD and *Cbp*S436A mice hippocampal DG and human post-mortem AD hippocampal DG tissues. (A) Images of 12-month-old Non-Tg and 3xTg-AD hippocampal DG sections immunostained for Mgll with DAB staining (n=2 animals/genotype). (B) Images of hippocampal DG (SGZ/GCL layers) sections from 3-monthold and 6-month-old WT mice, immunostained for Sox2 (red), NeuN (purple) and p-aPKC (green) and counterstained with Hoechst (blue). Arrows denote NeuN+ or Sox2+ cells; scale bar: 25 µm. (C) Images of hippocampal DG sections from 6-month-old WT and *Cbp*S436A mice, immunostained for Mgll (green) and counterstained with Hoechst (blue). Arrows denote Mgll+ cells; scale bar: 25 µm. (D) Images of human hippocampal DG sections from AD patients and their age-matched healthy controls (79-89 years) following Mgll immunohistochemistry with DAB staining. Arrows denote Mgll+ DAB stained cells. Scale bar: 50 µm.



Figure S2. JZL 184 and metformin does not significantly change general motor activities of WT and *Cbp***S436A, and Non-Tg and 3xTg-AD mice, respectively.** (A-B) Analysis of the total distance travelled and the mean velocity during short-term MWM probe test (A, day 5) and longterm MWM probe test (B, day 11) for 6-month WT and *Cbp*S436A mice that received either vehicle or JZL 184 treatment. (C-D) Analysis of the total distance travelled and the mean velocity during short-term MWM probe test (C, day 5) and long-term MWM probe test (D, day 11) for Non-Tg and 3xTg-AD mice that received either control or metformin treatment.





Figure S3. Metformin treatment removes intracellular β-amyloid accumulation from 3xTg hippocampal dentate gyrus. (A-B) Quantification by densitometry of β-amyloid (Aβ) immunoreactivity in the hippocampal dentate gyrus as in A; measurements were normalized to one of sections from Non-Tg/control group. (n=20-30 section/group). Data analysis was performed using one-way ANOVA (F (2,136) = 34.42, P< 0.0001, n=139) *** p < 0.001. Scale bar: 100 µm.



Figure S4. (A) ChIP-qPCR analysis for CBP binding at Mgll promoter in differentiating WT and *Cbp*S436A NPCs in the presence of metformin. ChIP analysis was performed to analyze the enrichment of CBP at the *Mgll* promoter. IgHy enhancer was used as a negative control. (n=3 animals/group). (B-D) Efficiency of shRNA-mediated Mgll knockdown. (B) Schematic representing Mgll shRNAs target regions. (C) Representative western blot images of total protein lysates from NIH3T3 cells transfected with *Mgll* shRNAs and a Scr shRNA, probed for Mgll and GAPDH (a loading control). (D) Quantitative analysis of Mgll expression in NIH3T3 cells 48 h after shRNA transfection, normalized to GAPDH. Data from 3 independent experiments was analyzed using one-way ANOVA (F(3, 8) = 10.09, P = 0.0043) with Dunnett's post-hoc test. * P < 0.05, ** P < 0.01. (Scr sh: Scramble shRNA; Mgll sh1: Mgll shRNA 1; Mgll sh2: Mgll shRNA 2).



Figure S5. Continued passaging does not change total aPKC protein levels. (A)

Representative western blot images of total protein lysates from proliferating P2 (early passage) and P5 (late passage) WT and *Cbp*S436A NPCs, probed for total aPKC and GAPDH (a loading control) from experiment1 (top panel) and 2 (bottom panel). (B) Quantitative analysis of total aPKC expression, relative to GAPDH in proliferating P2 and P5 WT and *Cbp*S436A NPCs. Data was normalised to corresponding P2 NPCs for each genotype.



Figure S6. AMPK protein expression in 3xTg-AD and Non-Tg NPCs. Immunofluorescent images of cultured P2 NPCs from 3xTg-AD and Non-Tg mice, immunostained for Sox2 (red) and AMPK (green), counterstained for Hoechst (blue). Negative control for IHC image was from 3xTg-AD NPCs that received only secondary antibody incubation. Scale bar: 50 µm.

		Age	sex	post-morte	em (hour)	
Healthy control	C-1	61	М	12		
	C-2	75	М	24		
	C-3	81	F	18		
	C-4	80	F	18		
	C-5	89	М	20		
AD patients	AD-1	59	М	4		
	AD-2	70	М	26		
	AD-3	76	М	24		
	AD-4	79	F	9		
	AD-5	81	F	6		
	AD-6	84	М	13		

Table S1. Human post-mortem samples information regarding age, sex and post-mortem

delay in tissue fixation. Human DG sections were stored in antifreeze solution (40% PBS, 30% Glycerol) at -20°C.

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	Wall Mki67 Mki67 Nkain2 Nr4a1 Pik Pcp41 Per1 Pmip1 Prc1 Sh3bp5 Sic6a15 Sytl2 Tagin3 Thy1 Top2a Wbscr17 Wisp2 Zic1 Zic2	1.1249 1.1249 1.1249 1.1372 1.7302 0.94843 -0.75427 1.9929 -1.53676 1.07927 0.87338 0.91302 1.02941	ENSMUSG0000033174 ENSMUSG0000031004 ENSMUSG000002303 ENSMUSG0000022033 ENSMUSG000002203 ENSMUSG000002203 ENSMUSG0000024521 ENSMUSG0000024521 ENSMUSG0000024521 ENSMUSG000002452 ENSMUSG000002452 ENSMUSG0000036460 ENSMUSG0000036460 ENSMUSG000003640 ENSMUSG0000026347 ENSMUSG00000226347 ENSMUSG00000226347 ENSMUSG000002404 ENSMUSG0000023400	Mus musculus Mus musculus	monoglyceride lipse antigen identified by monoclonal antibody Ki 67 Nav K/K transporting ATase interacting 2 nuclear receptor subfamily 4, group A, member 1 PDZ binding kinase Purkinje cell protein 1-4like 1 period homolog 1 (Drosophila) phoshoglucomutase 5 phohol 12-myristate 13-acetate-induced protein 1 protein regulator of cytokinesis 1 protein protein 1, cellular SH3-domain binding protein 5 (BTK-associated) solute carrier family 6 (neurotransmitter transporter), member 15 synaptotagmin-like 2 transgelin 3 thymus cell antigen 1, theta hyposthelia protein 1.celloa/7091; transmembrane protein 163 toposineerase (DNA) II al pha WITI inducible signaling protein 1 WITI inducible signaling protein 1 / binolog (human); similar to UDP-GaINAc:polypeptide N-acetylgalactosaminyltransferase-like 3 WITI inducible signaling protein 0 / bin cerebellum 1 zinc finger protein of the cerebellum 1

 Table S2. RNA-seq analysis from differentiating WT and CbpS436A NPCs in the presence

of metformin for 6 days.