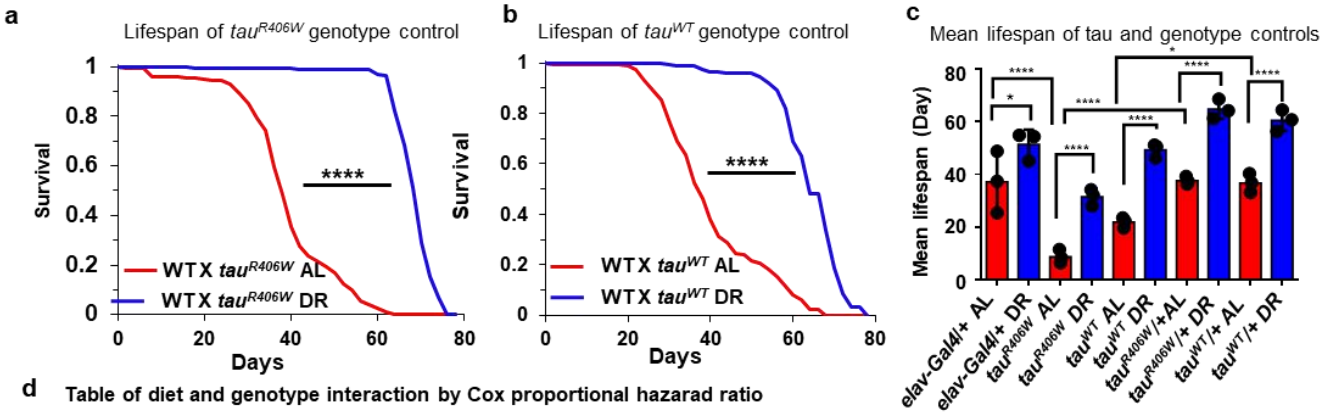
Supplemental Information

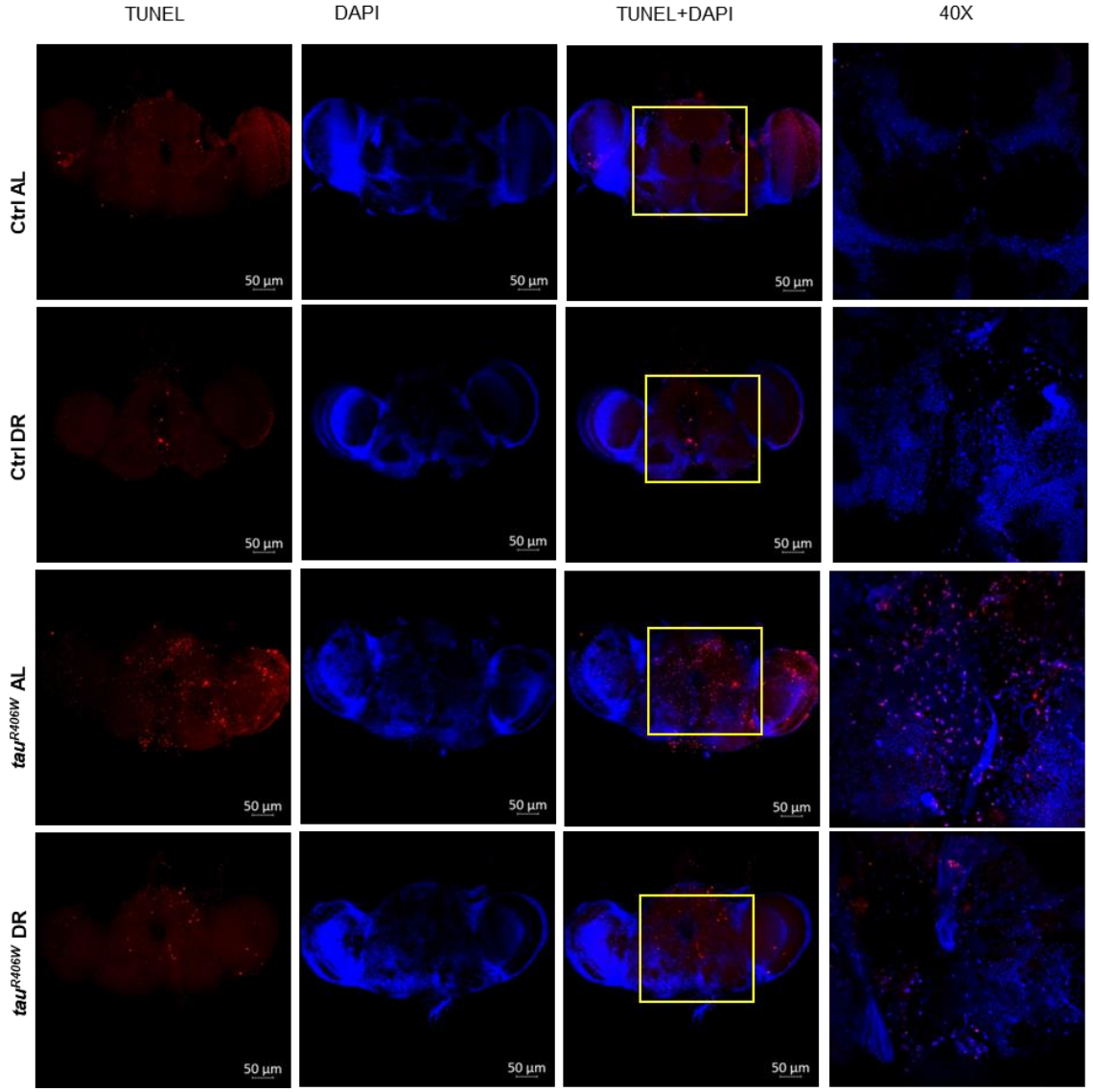
Supplementary Data Figures & Figure Legends



d Table of diet and genotype interaction by Cox proportional hazarad ratio

Interactor	coef	exp(coef)	se(coef)	z	Pr(>|z|)	
tau^{R406}	2.290126	9.876178	0.118034	19.402	<2.00E-16	***
diet	-1.12847	0.323526	0.171896	-6.565	5.21E-11	***
elav	1.303901	3.683638	0.084238	15.479	<2.00E-16	***
tau^{WT}	1.826239	6.210486	0.1164	15.689	<2.00E-16	***
tau^{R406}:diet	-0.91141	0.401958	0.164682	-5.534	3.12E-08	***
diet:*elav*	-0.00226	0.997739	0.11947	-0.019	0.985	ns
diet:*tau*^{WT}	-0.705	0.494106	0.160715	-4.387	1.15E-05	***

e Apoptotic cell death in of *tau*^{R406W} fly brain



Extended Data Fig. 1

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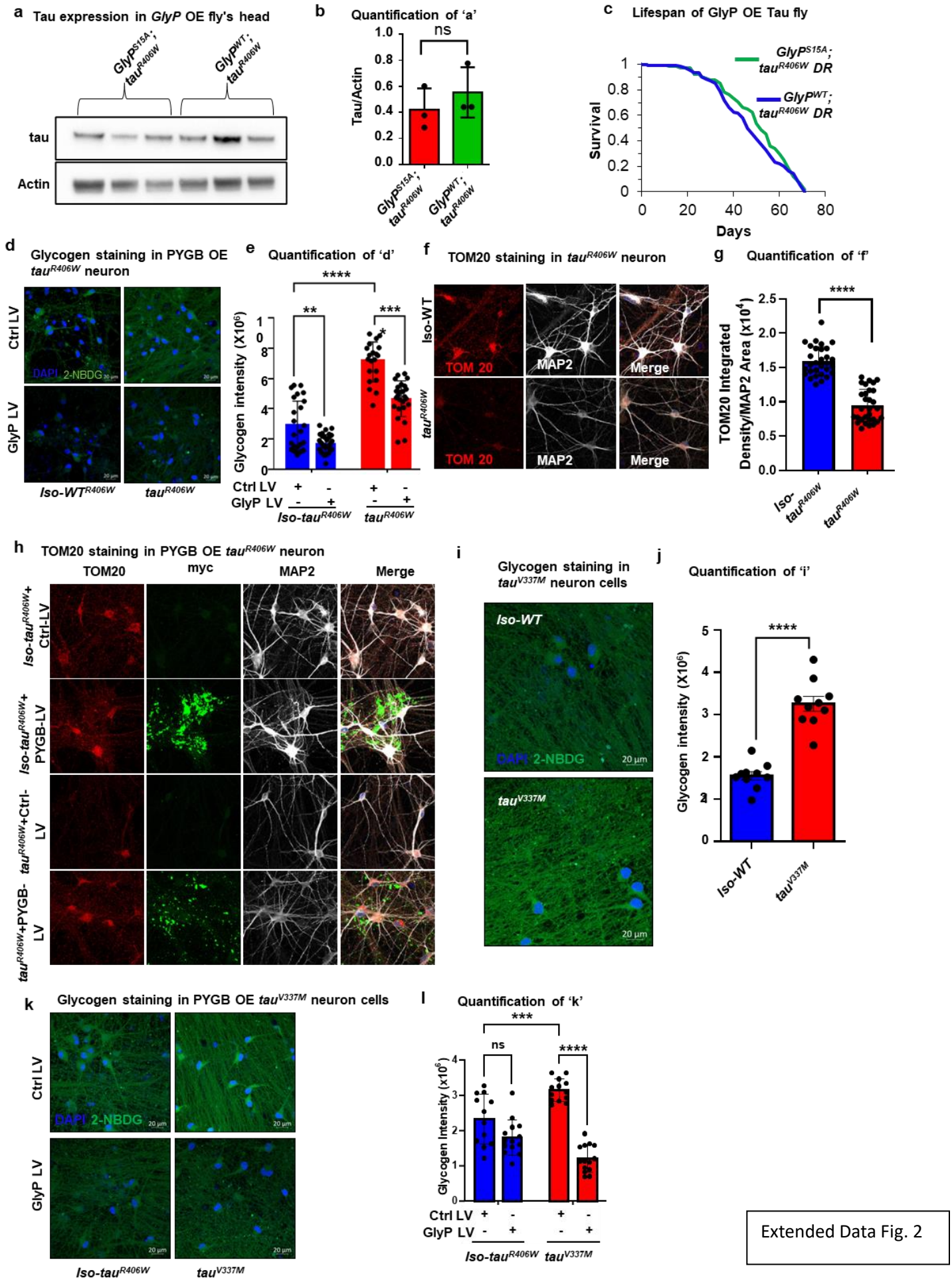
a, Lifespan of control flies (W^{1118} crossed with tau^{R406W}) shows DR-mediated extension. **b**, Lifespan of control flies (W^{1118} crossed with tau^{WT}) shows DR-mediated extension**. c,** Mean lifespan of controls, $tau^{R406W,}$ and tau^{WT} of 3 independent experiments show lifespan extension by DR. Tau^{WT} and tau^{R406W} flies have the shortest lifespan than controls. **d**, Table shows the result of Cox Proportional hazard ratio test. The coefficient (coef) is that term's beta value, with values >0 meaning that term increases the hazard (risk of death), and values of <0 decreasing the hazard (risk of death). The term exp(coef) is that term's hazard ratio (HR), with the following breakdown: HR = 1: No effect, HR < 1: Reduction in the hazard, HR > 1: Increase in Hazard. The term se(coef) is the standard error for that term. The z term gives the Wald statistic value. It corresponds to the ratio of each regression coefficient to its standard error (z = coef/se(coef)). The Wald statistic evaluates whether the coef is statistically different from 0. The final term, Pr(>|z|), is that row's p-value. The rest of the table gives the confidence intervals for each variable. **e**, Apoptotic cell death detected by TUNEL staining in tau^{R406W} fly whole brain shows increased TUNEL staining in tau^{R406W}. An asterisk (*) indicates a significant difference between experimental groups and controls, with the level of significance denoted by the number of asterisks $p < 0.05$ for *, $p < 0.01$ for **, $p < 0.001$ for *** and $p < 0.0001$ for **** by log-rank test (a and b) or by oneway ANOVA (c). Data in bar graphs are presented as mean ± SEM.



Extended Data Fig. 2

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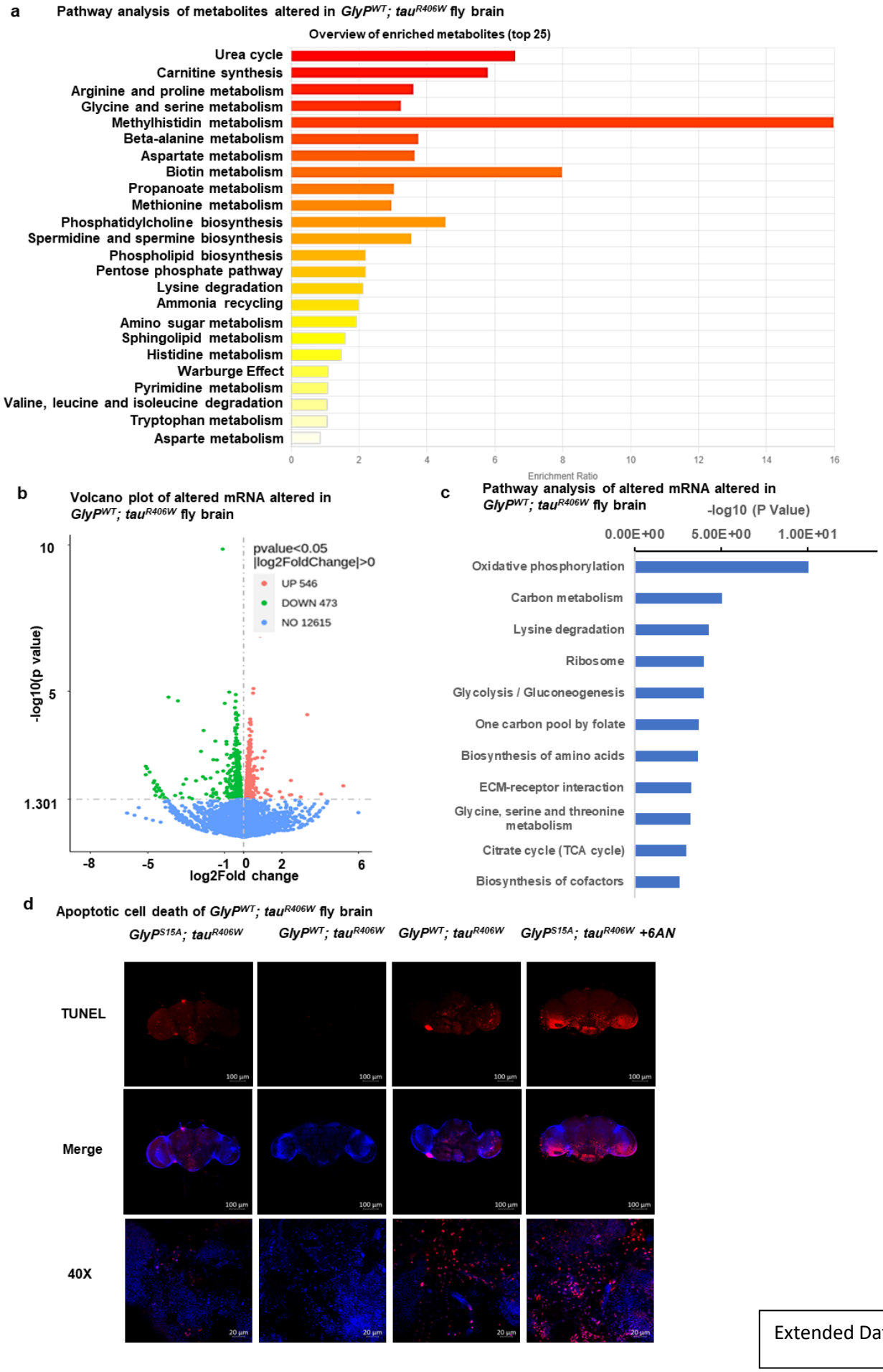
a, Western blot shows tau expression in *GlyP^{S15A}; tau^{R406W,}* and GlyP^{WT}. **b,** Densitometric analysis of tau expression is not changed between *GlyP^{S15A}; tau^{R406W}* and *GlyP^{WT}; tau^{R406W}*. **c**, Lifespan of *GlyP^{WT}; tau^{R406W}* and *GlyP^{S15A}; tau^{R406W}* shows no significant difference. **d**. Images show glycogen staining in iPSC-derived Tau^{R406W} and isogenic control (Iso-WT) neurons by 2-NBDG. **e,** Quantification of glycogen staining shows glycogen staining increase in control virus-infected *tau^{R406W}* than isogenic control transfected with control lentivirus, and the glycogen staining is reduced in *tau^{R406W}* cells with *PYGB* overexpression. **f**, TOM20 staining of iPSC-generated neurons shows reduced mitochondrial density in *tau^{R406W}* than isogenic control cells. **g**, Quantification of TOM20 staining **h**, TOM20 staining in *PYGB* overexpressing *tau^{R406W}* cells show reduced mitochondrial staining in control lentivirus transduction while mitochondrial density is rescued by *PYGB* containing lentivirus. **i**, Glycogen staining with 2-NBDG in iPSC-generated *tau^{V337M}* neurons and its isogenic control. **j**, Quantification shows increased glycogen staining in *tau^{V337M}* cells. **k**, Glycogen staining in Tau^{V337M} cells and its isogenic control. **l**, Quantification shows *PYGB* overexpression reduces glycogen staining in *tau^{V337M}* cells more than its control cells with control lentivirus. An asterisk (*) indicates a significant difference between experimental groups and controls, with the level of significance denoted by the number of asterisks $p < 0.05$ for *, $p < 0.01$ for **, $p < 0.001$ for *** and $p < 0.0001$ for **** by Student's t-Test (b, g, and j) or by oneway ANOVA (e and l). Data in bar graphs are presented as mean ± SEM.



Extended Data Fig. 3

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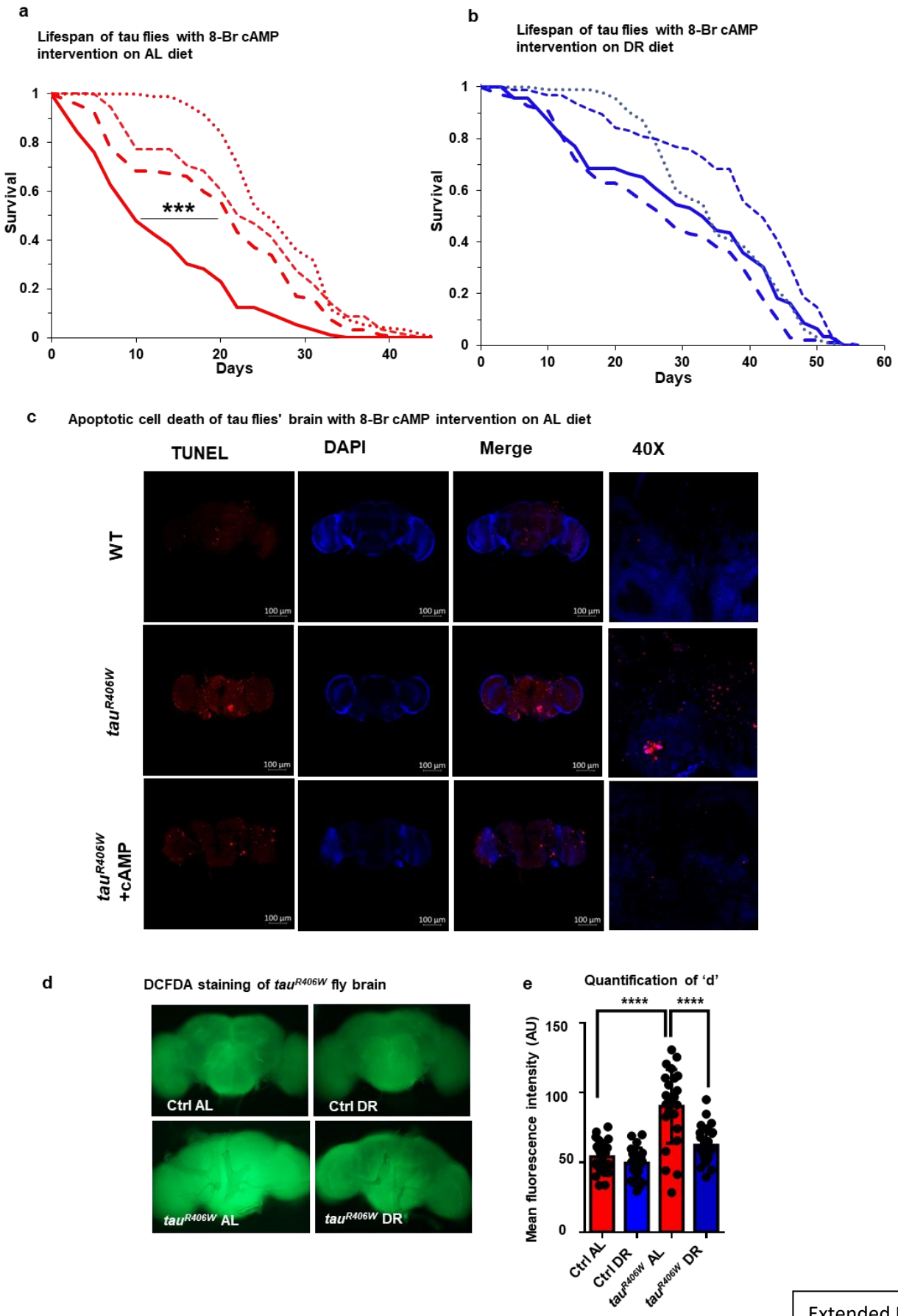
a, Pathway analysis of metabolites shows amino acids metabolism, urea cycle, and PPP are the few most common pathways. in *GlyP^{WT}; tau^{R406W}* in comparison with *GlyP^{S15A}; tau^{R406W}*. **b**, Volcano plot shows 546 transcripts (red) are upregulated and 473 transcripts (green) are down-regulated. **c**, Pathway analysis of altered RNA shows oxidative phosphorylation, glycolysis or gluconeogenesis, ECM- receptor interaction and TCA cycle are the most common. **d**, TUNEL staining of *GlyP^{WT}; tau^{R406W}* with 6-AN treatment shows *GlyP^{WT}* mediated reversal of apoptotic death of brains abrogate by 6-AN treatment.



Extended Data Fig. 4

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a, Lifespan extension of *tau*^{R406W} on AL diet with 8-Br-cAMP treatment is more than other control flies. **b**, Lifespan of *tau*^{R406W} on DR diet with 8-Br-cAMP shows no extension further DR-mediated extension. **c**, TUNEL staining shows cAMP treatment rescues apoptotic cells in *tau*^{R406W} fly brain. **d**, Images of the whole-mount brain with DCFDA staining of control and *tau*^{R406W} on AL and DR. **e**, Quantification shows increased ROS stained by DCFDA in *tau*^{R406W} flies' brain which is rescued by DR. An asterisk (*) indicates a significant difference between experimental groups and controls, with the level of significance denoted by the number of asterisks $p < 0.05$ for *, $p < 0.01$ for **, $p < 0.001$ for *** and $p < 0.0001$ for **** by log-rank test (a&b) or by oneway ANOVA (e). Data in bar graphs are presented as mean ± SEM.

Supplementary Data Table 1

GO term of up regulated proteins		
Term ID	**Term description**	**False discovery rate**
GO:0019752	Carboxylic acid metabolic process	2.12E-07
GO:0044281	Small molecule metabolic process	2.56E-07
GO:0009987	Cellular process	4.49E-07
GO:0008152	Metabolic process	2.53E-06
GO:0055114	Oxidation-reduction process	7.86E-06
GO:0065008	Regulation of biological quality	3.12E-05
GO:0032787	Monocarboxylic acid metabolic process	3.15E-05
GO:0005977	Glycogen metabolic process	5.32E-05
GO:0006631	Fatty acid metabolic process	5.32E-05
GO:0009605	Response to external stimulus	5.55E-05
GO:0005975	Carbohydrate metabolic process	6.26E-05
GO:0071704	Organic substance metabolic process	9.16E-05
GO:0006091	Generation of precursor metabolites and energy	0.00016
GO:0044237	Cellular metabolic process	0.00016
GO:0015980	Energy derivation by oxidation	0.00017
GO:0044238	Primary metabolic process	0.00017
GO:0009058	Biosynthetic process	0.00021
GO:0044248	Cellular catabolic process	0.00028
GO:0046394	Carboxylic acid biosynthetic process	0.00031
GO:0042221	Response to chemical	0.00048
GO:0010033	Response to organic substance	0.00079
GO:0044283	Small molecule biosynthetic process	0.00096
GO:0035158	Regulation of tube diameter, open tracheal system	0.0011
GO:1901576	Organic substance biosynthetic process	0.0011

GO term of down regulated proteins		
Term ID	**Biological process**	**False discovery rate**
GO:0046034	ATP metabolic process	6.66E-25
GO:0022900	Electron transport chain	1.77E-20
GO:0006119	Oxidative phosphorylation	1.48E-18
GO:0022904	Respiratory electron transport chain	1.48E-18
GO:0042775	Mitochondrial ATP synthesis coupled electron transport	1.48E-18
GO:0006091	Generation of precursor metabolites and energy	9.81E-18
GO:0055114	Oxidation-reduction process	4.64E-17
GO:0045333	Cellular respiration	9.31E-17
GO:0009987	Cellular process	1.01E-15
GO:0006120	Mitochondrial electron transport, NADH to ubiquinone	7.46E-14
GO:0006796	Phosphate-containing compound metabolic process	5.63E-11
GO:0044237	Cellular metabolic process	3.15E-10
GO:0016310	Phosphorylation	3.27E-10
GO:1902600	Proton transmembrane transport	8.85E-10
GO:0009141	Nucleoside triphosphate metabolic process	9.05E-09
GO:0009142	Nucleoside triphosphate biosynthetic process	5.28E-08
GO:0009206	Purine ribonucleoside triphosphate biosynthetic process	1.4E-07
GO:0015986	ATP synthesis coupled proton transport	3.77E-07
GO:0008152	Metabolic process	1.14E-06
GO:0002181	Cytoplasmic translation	1.67E-06
GO:0006753	Nucleoside phosphate metabolic process	2.92E-06
GO:0015672	Monovalent inorganic cation transport	3.48E-06
GO:0098754	Detoxification	3.48E-06
GO:0098662	Inorganic cation transmembrane transport	3.78E-06

The Table shows GO term of upregulated and down regulated proteins. The highlighted rows indicate that glycogen metabolism is one of the enriched pathways for upregulated proteins while oxidative phosphorylation and detoxification are enriched among down regulated proteins.