

Serotonergic Upregulation Rescues Pathological Circadian Deficits in a Drosophila Model of Amyloid Toxicity.

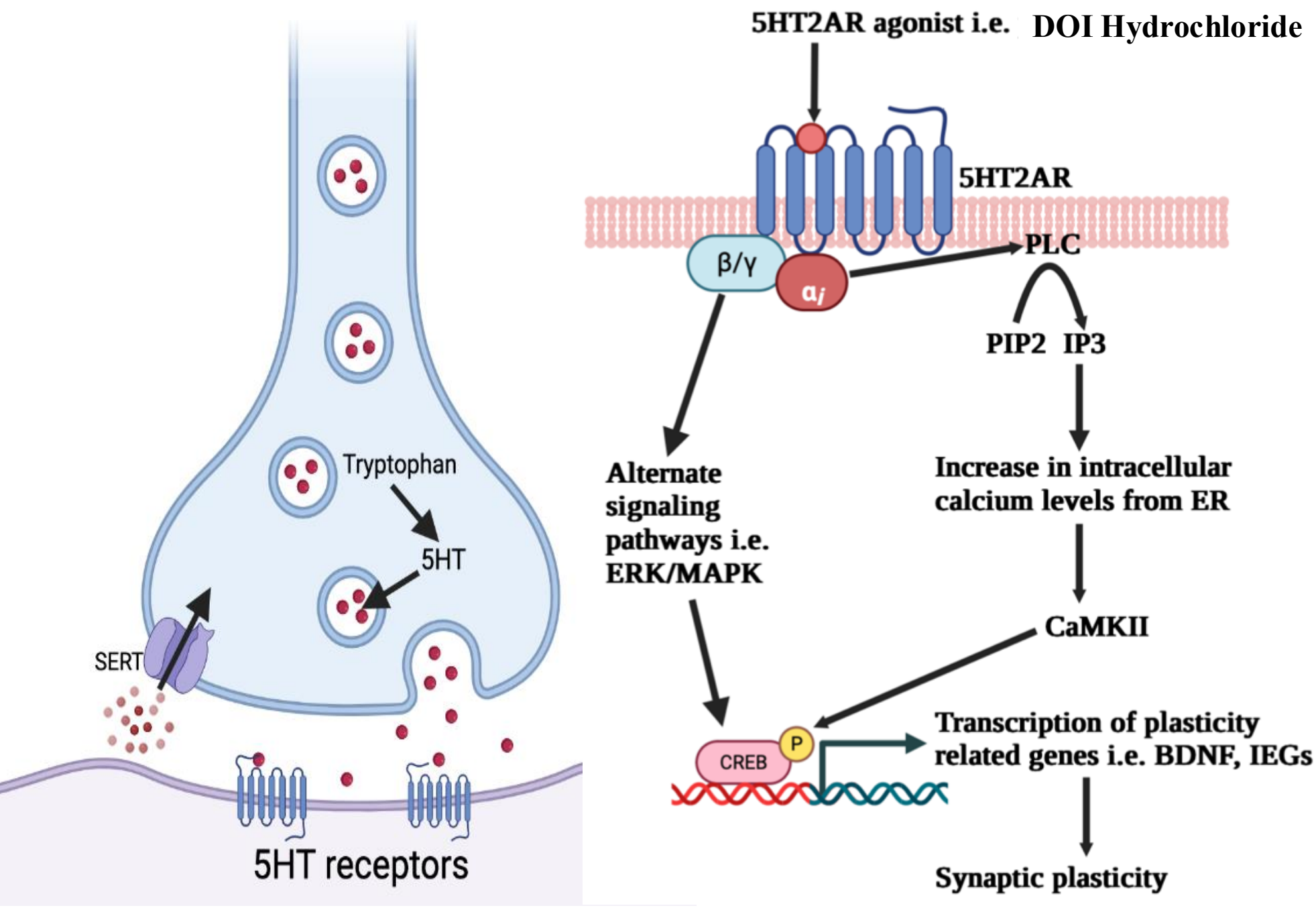
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Background

- The serotonergic (5HT) neurotransmitter system exhibits one of the most pronounced impairments in Alzheimer's Disease (AD), including deficits in serotonin levels [1] and 5HT receptors, particularly the 2A [2] and 1A subtypes [3].
- Activation of 5HT2A is known to stimulate neuroplastic changes [4].
- Neuroplasticity is severely impaired in AD, making neuroplasticity-enhancing targets promising therapeutic strategies for neurodegeneration.



5HT is an evolutionary conserved neurotransmitter and neuromodulator. *Drosophila* have a simplified serotonergic system with a 106 5HT neurons in the adult CNS and homologues of the human 5HT receptor subtypes 1A, 1B, 2A, 2B and 7.

Simplified schematic illustrating the proposed molecular mechanism inducing synaptic plasticity downstream of 5HT2Ar. BDNF, brain derived neurotrophic factor; CaMKII, Ca²⁺/calmodulin-dependent protein kinase; CREB, cyclic AMP-responsive element binding protein; ER, endoplasmic reticulum; ERK, extracellular regulated kinase; IEG, immediate early genes; IP3, inositol triphosphate; MAPK, mitogen activated protein kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; 5HT2Ar, serotonin 2A receptor.

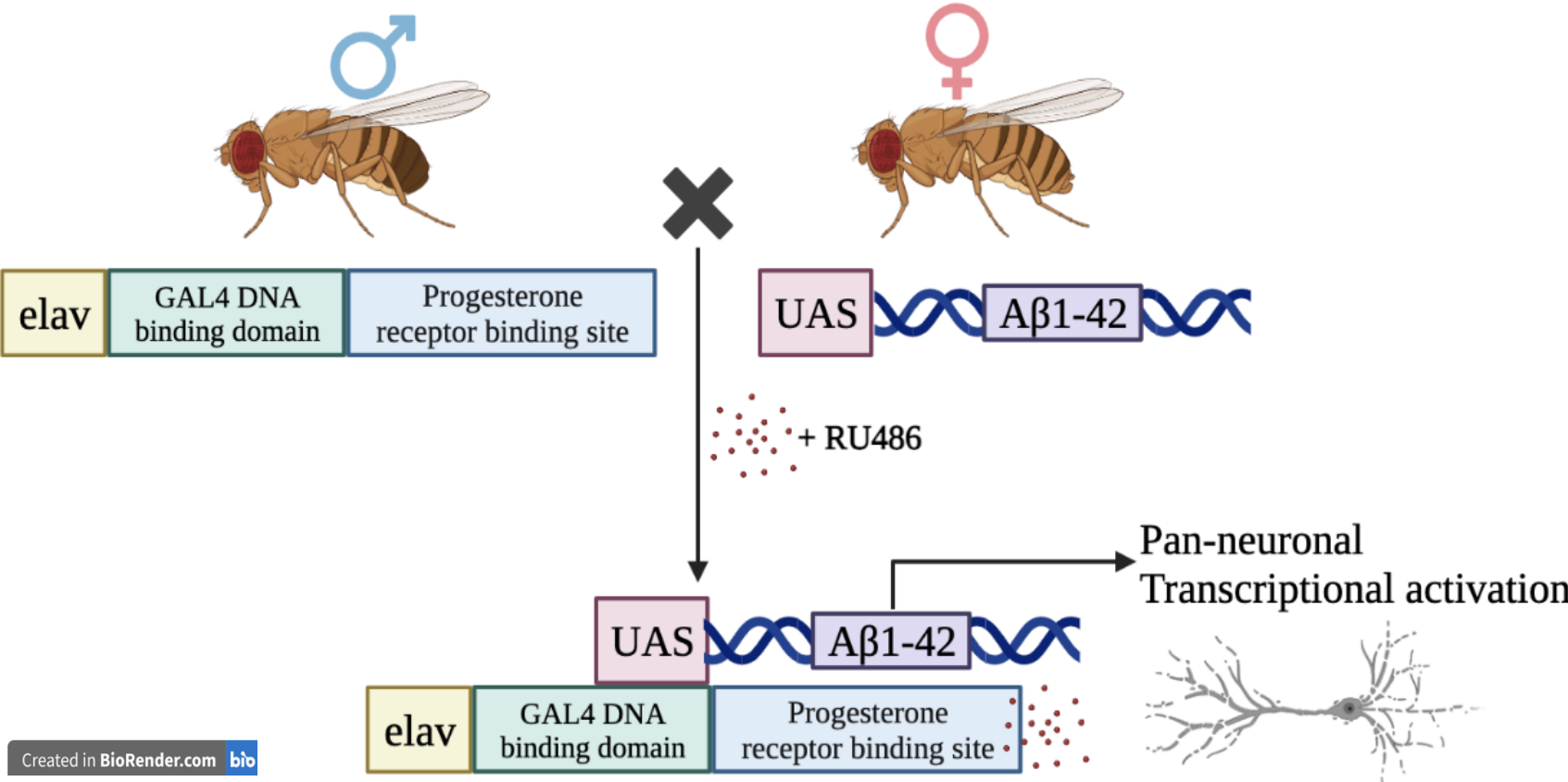
Aims

- Determine whether 5HT2A activation mitigates A β -induced pathological phenotypes, using a *Drosophila* model of amyloid toxicity, looking in particular at lifespan and sleep.

Methods

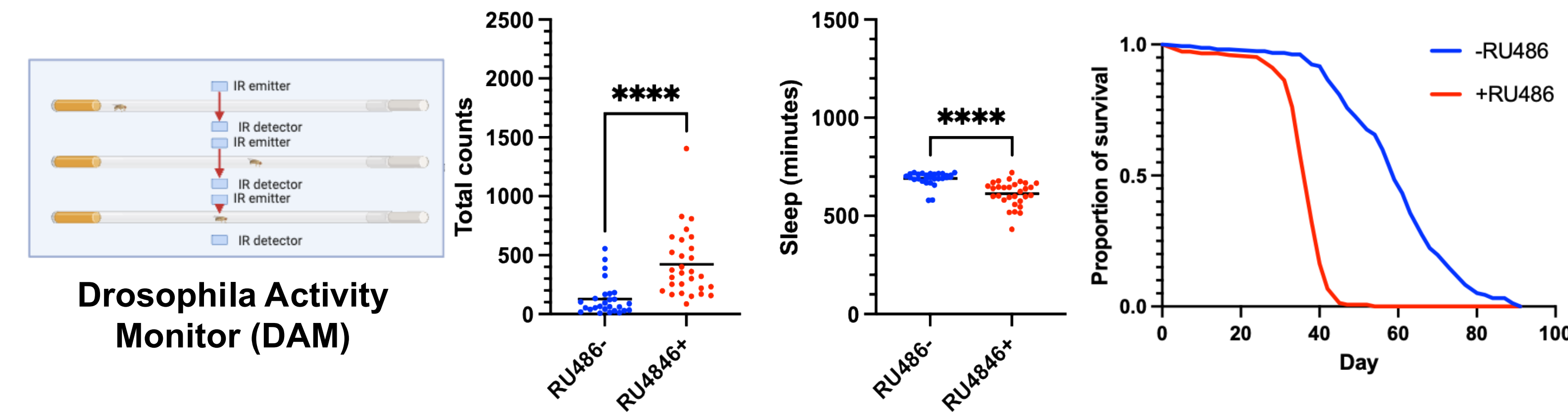
- The GeneSwitch GAL4 system was used to express 2 copies of human wild-type A β 1-42 specifically in the adult *Drosophila* brain following RU486 administration, which activates the progesterone receptor domain of the GeneSwitch GAL4 chimeric protein.
- Spatial control is achieved by a tissue-specific promoter.

Adult-Onset *Drosophila* model of A β 1-42 toxicity



UAS-A β 1-42 transgenic flies exhibit night-time hyperactivity (left) and sleep deficits (right).

- DAM is an automated system for continuous locomotor and sleep activity. Individual flies are sealed in tubes in which an infrared beam detects every cross of the tube midpoint.
- Activity = sum of number of crossings.
- Sleep = sum of continuous periods of inactivity (>5 minutes).

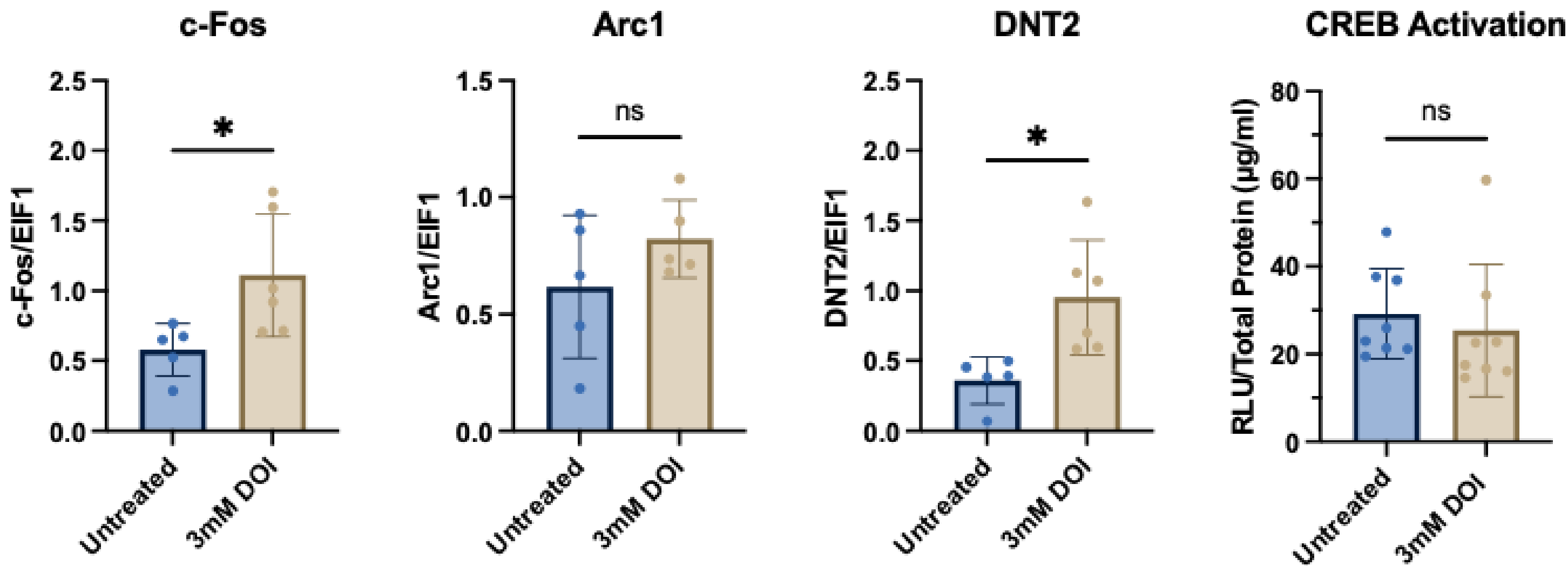


UAS-A β 1-42 transgenic flies exhibit a shortened lifespan

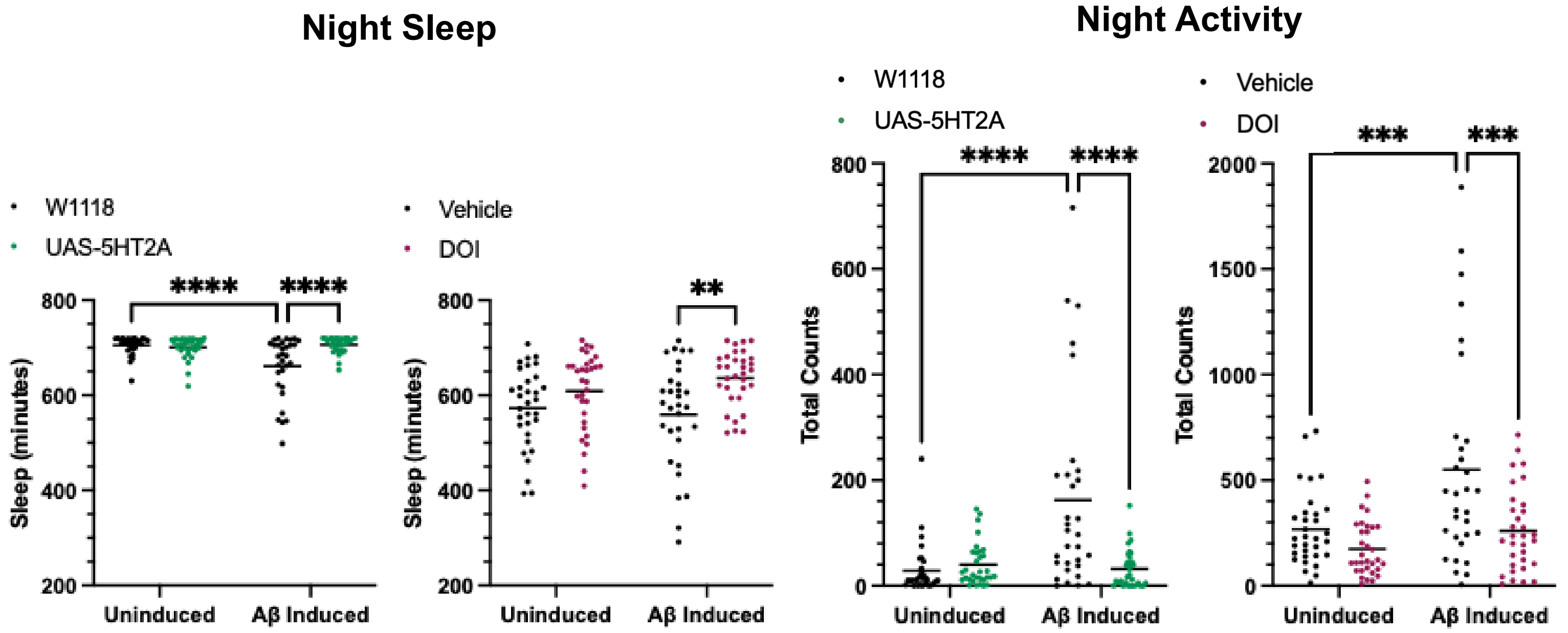
- Survival data is presented as cumulative survival curves with log-rank statistical comparisons.

Results

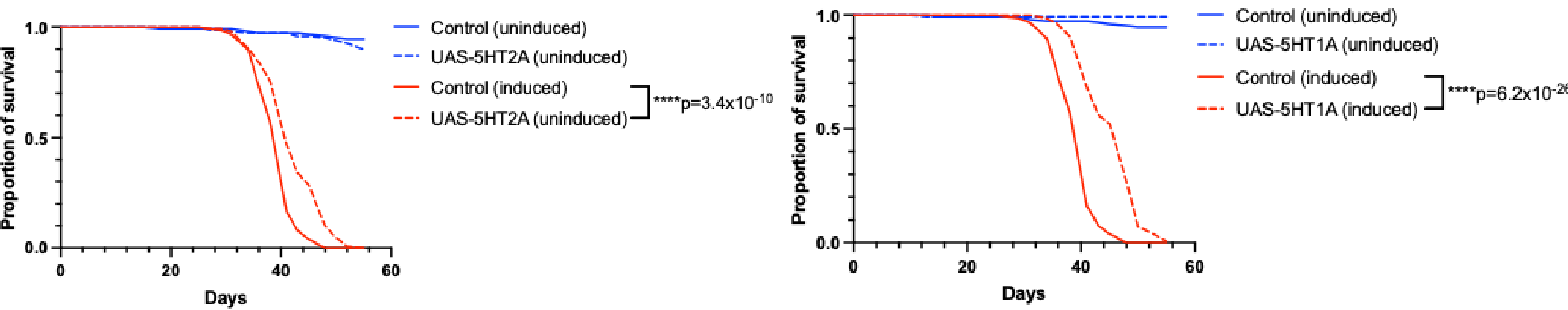
- Activation of 5HT2Ar recapitulates the mammalian 5HT2A-driven neuroplasticity promoting transcriptional signature in *Drosophila*, via a CREB-independent transcription factor.
- qPCR confirms 5HT2A-induced upregulation of the immediate early genes c-Fos and *Drosophila* Neurotrophic Factor (DNT2) which is the equivalent of human brain derived neurotrophic factor (BDNF).
- CRE (cAMP Response Element) luciferase assay revealed that unlike in mammalian systems [4], CREB is not activated via *Drosophila* 5HT2A.



Overexpression of 5HT2A and the Selective 5HT2A Agonist DOI Hydrochloride rescue A β 1-42-induced circadian-related phenotypes



Overexpression of 5HT2A and 5HT1A extends lifespan in the A β 1-42 model



Conclusion

- The results demonstrate that 5HT1A and 5HT2A activation partially ameliorates amyloid toxicity, with 2A specifically rescuing circadian-related deficits. The next steps include determining in more detail the underlying molecular mechanisms and immunofluorescent imaging to investigate related neuroplastic changes.

References

[1] Aral, H., et al. Changes of Biogenic Amines and Their Metabolites in Postmortem Brains from Patients with Alzheimer-Type Dementia. J Neurochem 43, (1984).
[2] Lai, MK., et al. Loss of serotonin 5-HT_{2A} receptors in the postmortem temporal cortex correlates with rate of cognitive decline in Alzheimer's disease. Psychopharmacology 179, (2005).
[3] Mattsson P., et al. Decreased 5-HT_{1A} binding in mild Alzheimer's disease—A positron emission tomography study. Synapse 76 (7-8), (2022).
[4] Desouza, L., et al. The Hallucinogenic Serotonin_{2A} Receptor Agonist, 2,5-Dimethoxy-4-Iodoamphetamine, Promotes cAMP Response Element Binding Protein-Dependent Gene Expression of Specific Plasticity-Associated Genes in the Rodent Neocortex. Front Mol Neurosci. 14:790213, (2021).

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