



NEUROPROTECTIVE EFFECTS OF THE CYCLOPHILIN D DEFICIENCY IN β -AMYLOID MOUSE MODEL

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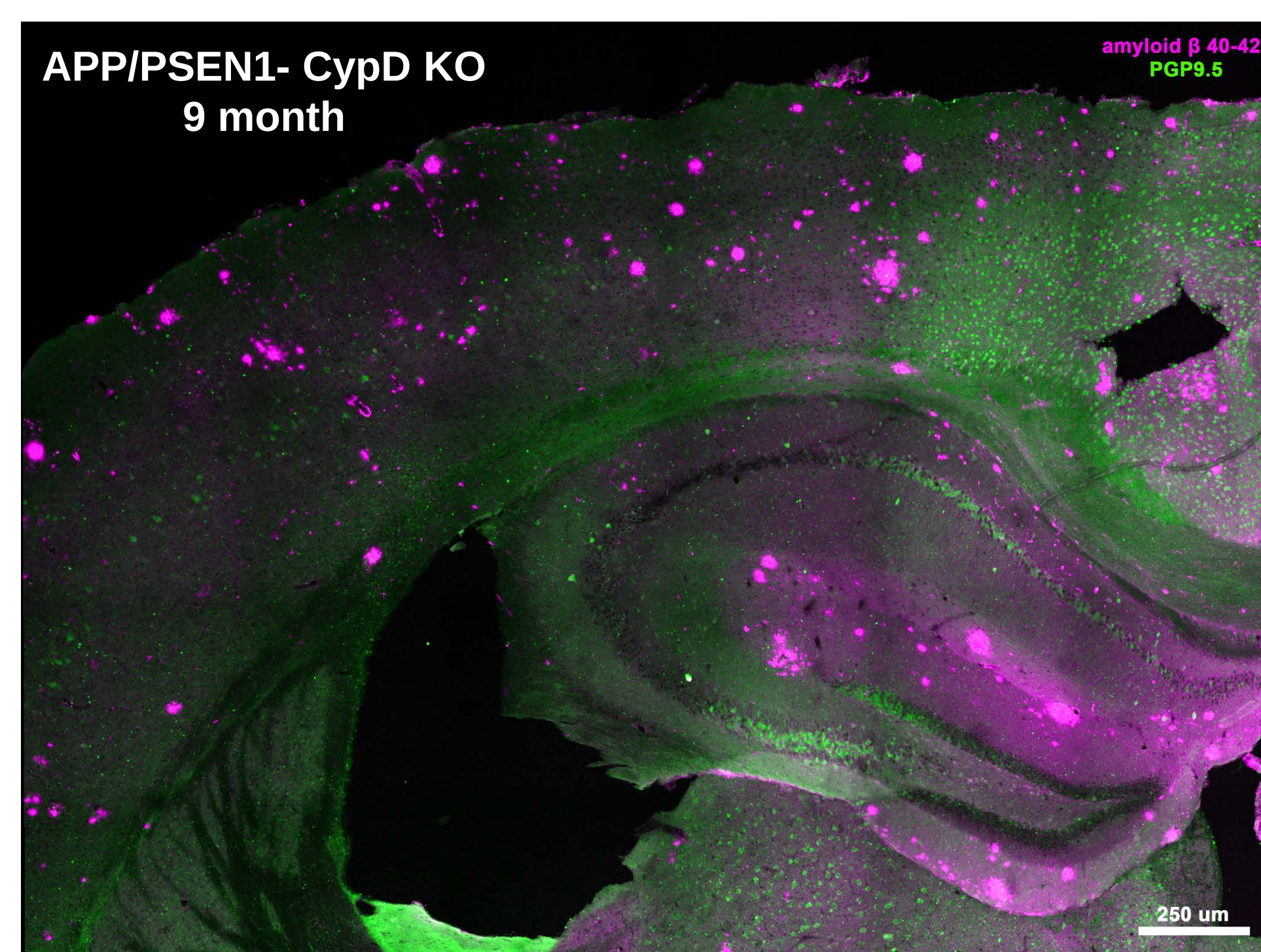
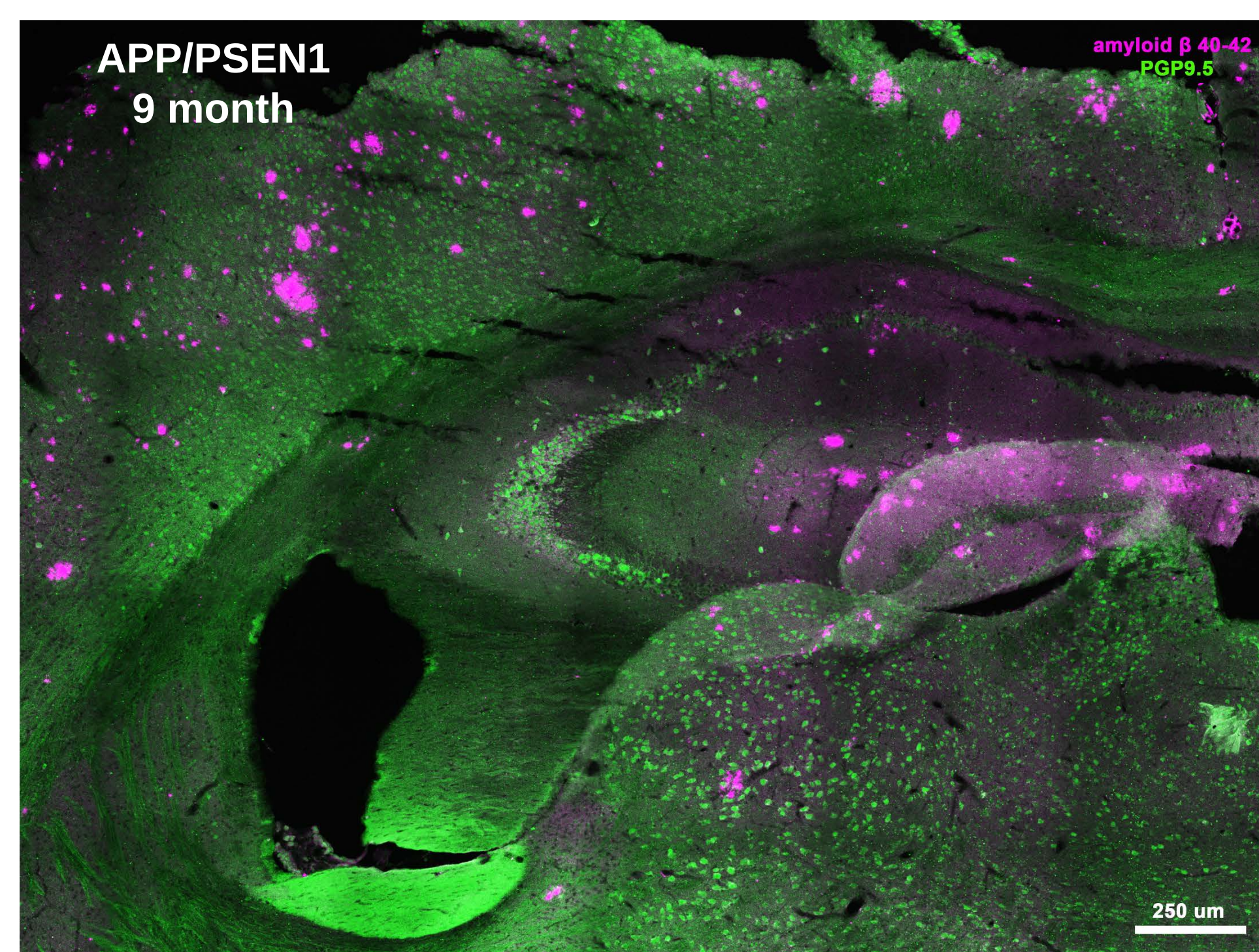
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Introduction

The accumulation of amyloid β ($A\beta$) and tau proteins in the brain is the fundamental of Alzheimer disease. In the early phase of the disease the $A\beta$ binds to the mitochondrial proteins and cause bioenergetic failure and increased oxidative stress, which can induce neuronal death. The mitochondrial cyclophilin D (CypD) protein is a major component and regulator of mitochondrial permeability transition pore. In our experiments the gene deletion of CypD (CypD KO) neuroprotective effects were investigated in the present of $A\beta$.

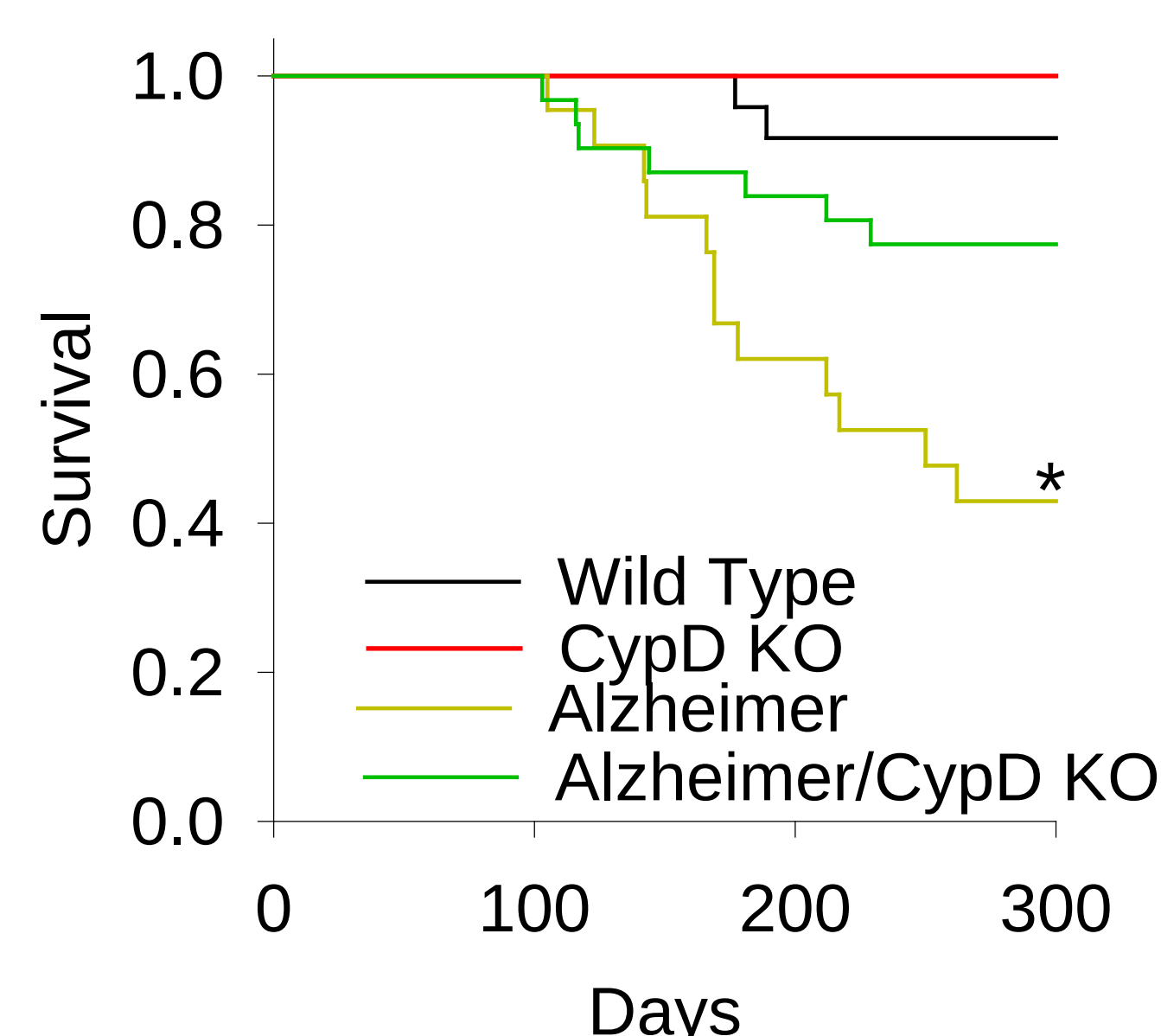
Our goal was to cross transgenic mice overexpressing a mutant human form of amyloid precursor protein (APP) and mutated presenilin1 (PSEN1) with CypD KO. In our experiments mitochondrial functions were examined.

Amyloid plaques detection with fluorescent immunohistochemistry



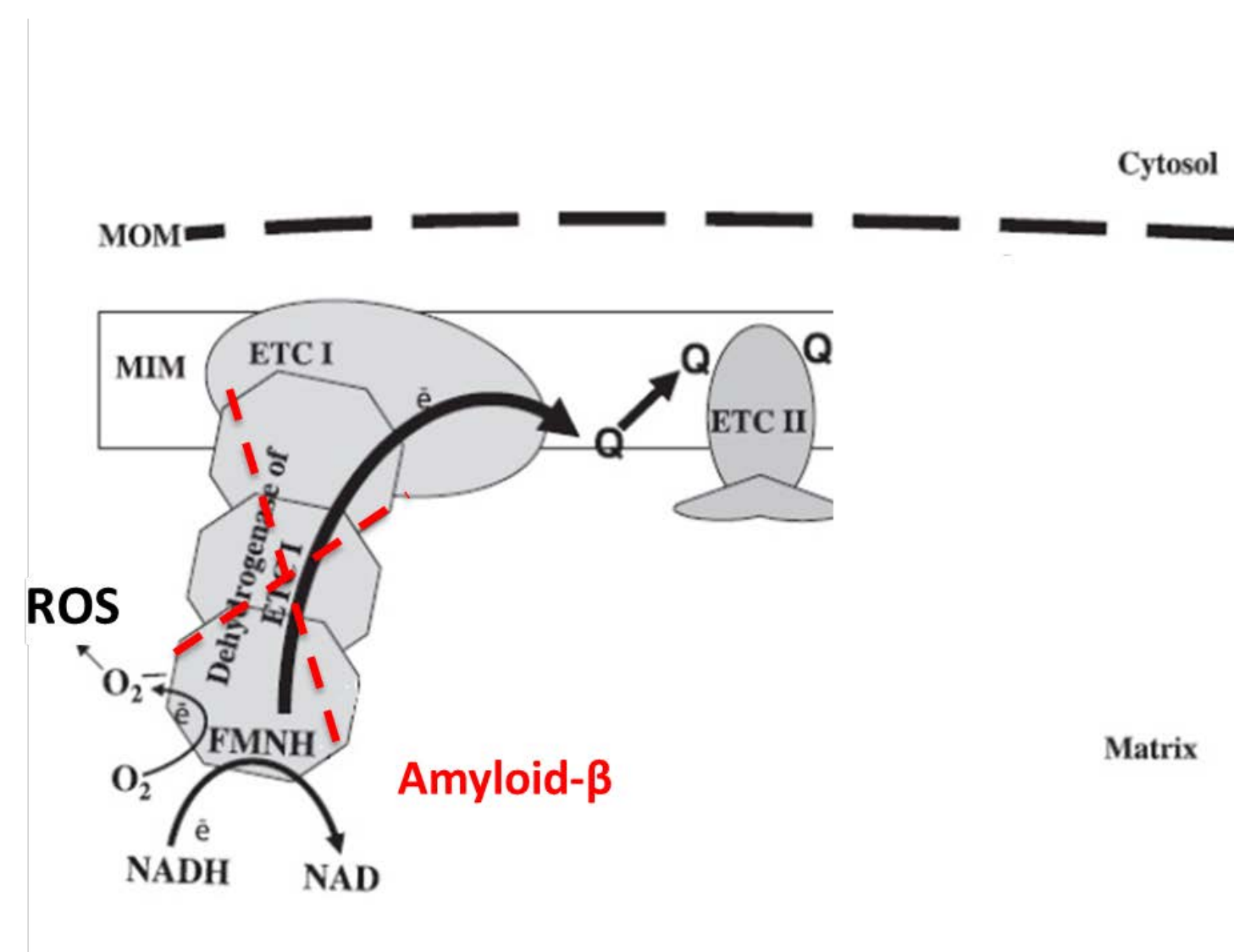
The amyloid plaques are presented in the cortex and hippocampus.

Survival analysis of four mice groups



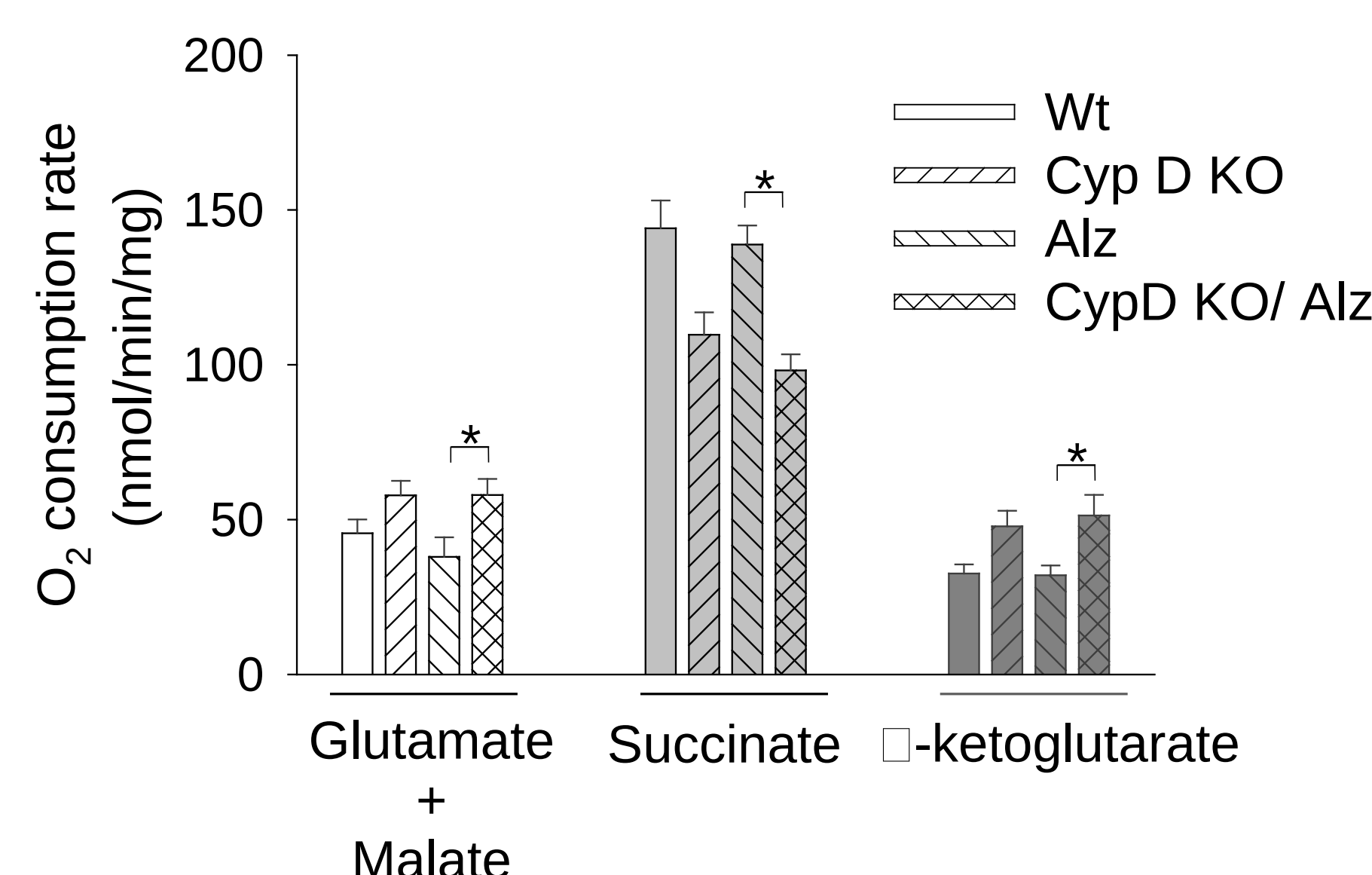
The mortality of the male Alzheimer's mice group increased. The knocking out cyclophilin D increased the survival.

β -amyloid postulated effect on the mitochondrial respiratory chain



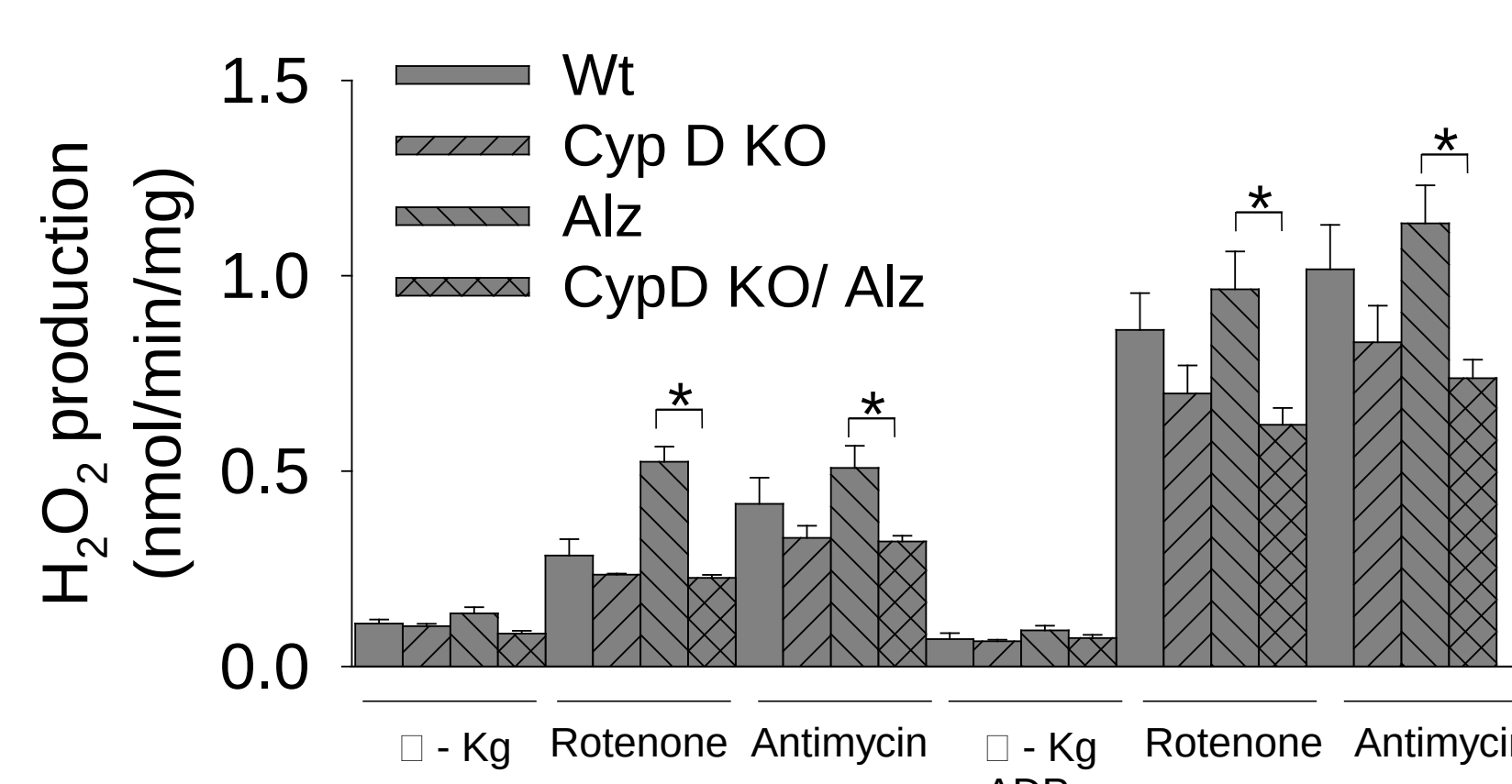
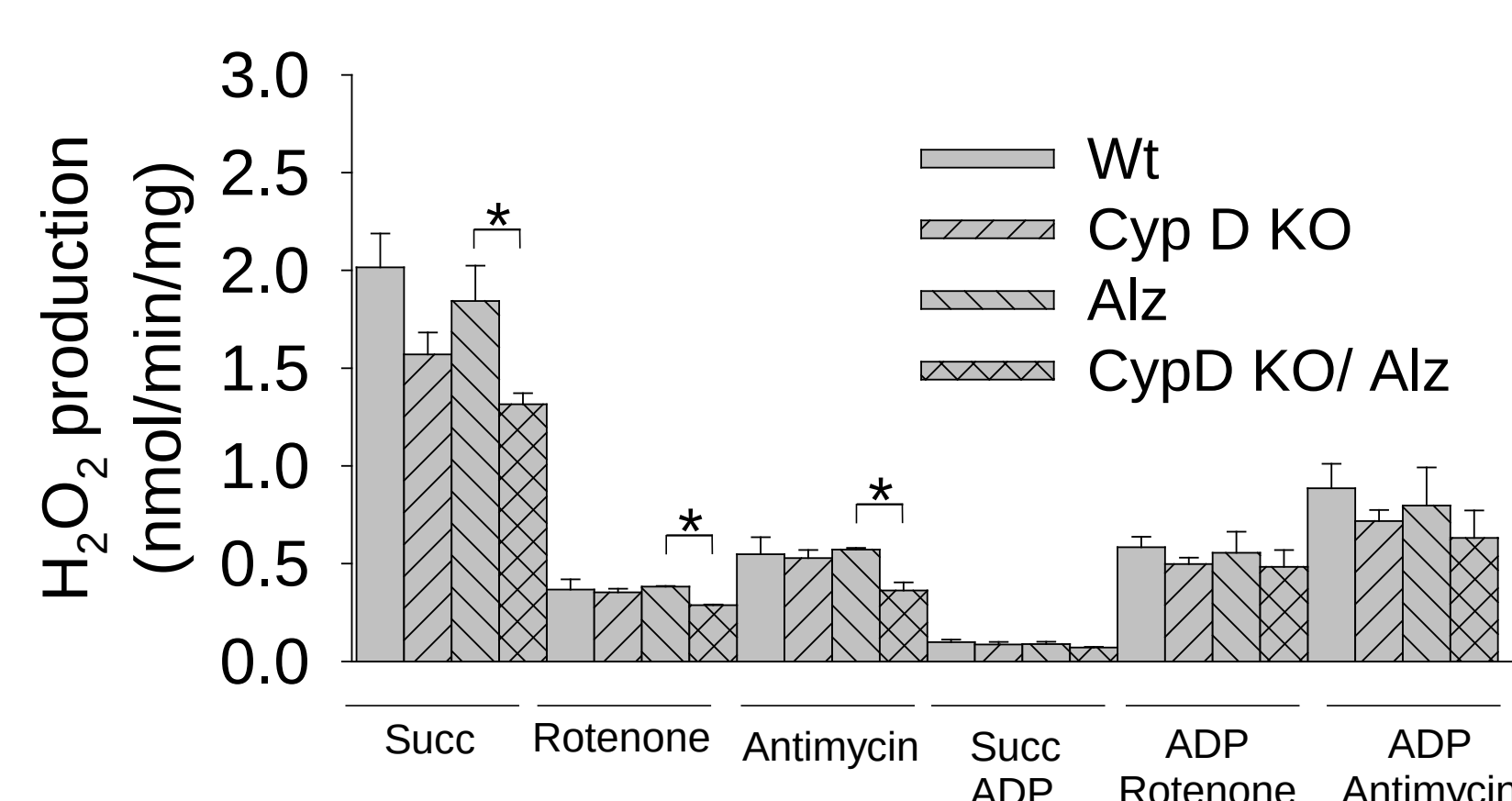
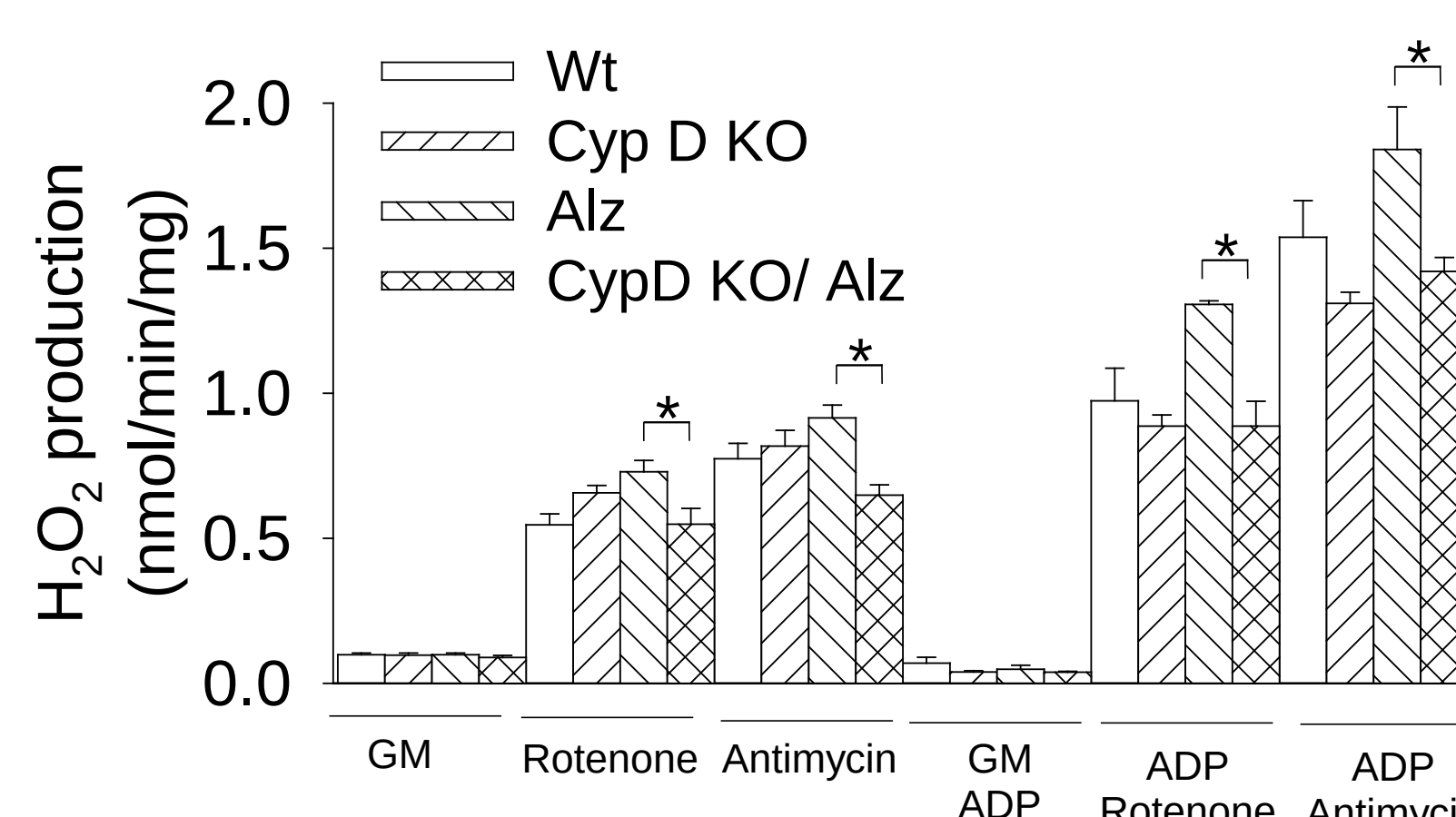
	O ₂ consumption	ATP production	ROS production
Alz	↓	↓	↑
Alz/CypD KO	↑	↑	↓
CypD KO	↑	↑	↓

Mitochondrial oxygen consumption with different respiratory substrates



Oxygen consumption decreased with NADH-dependent substrates in Alzheimer's mice mitochondria.

Mitochondrial ATP production with different respiratory substrates

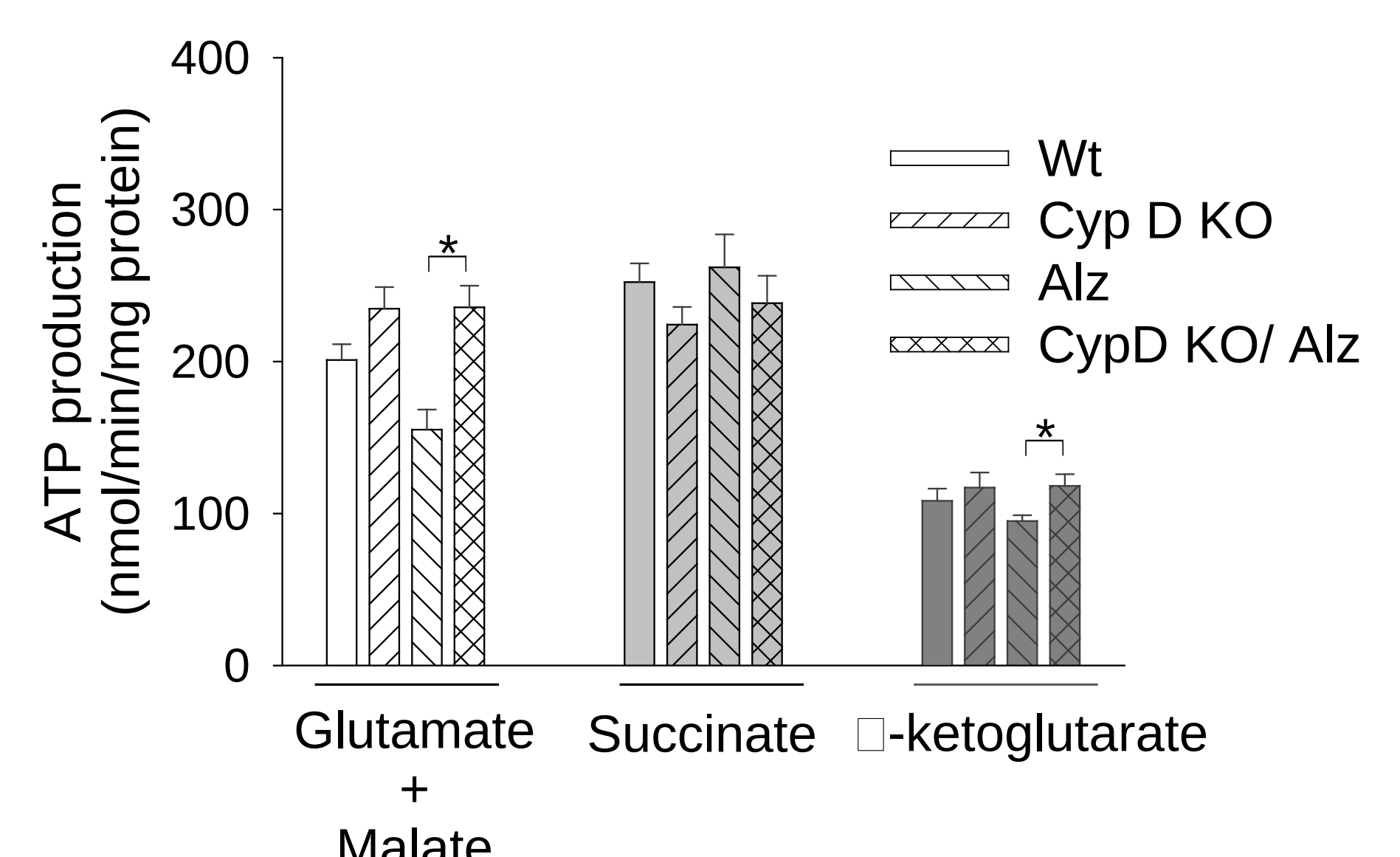


H₂O₂ production was increased in the Alzheimer's mice mitochondria and in the Cyclophilin D KO decreased it.

Results

- The amyloid plaques were present in the Alzheimer's and Alzheimer's/CypD KO mice.
- The knocking out of cyclophilin D increased the survival compared to the Alzheimer mice.
- The mitochondrial respiration was decreased with NADH-dependent substrates, but it was increased with succinate.
- Similar like the respiration the ATP production was also decreased with NADH-dependent substrates, but there was no difference with succinate.
- The mitochondrial H₂O₂ production was increased in the Alzheimer's mice mitochondria with NADH-dependent substrates and succinate also.

Mitochondrial ATP production with different respiratory substrates



ATP production decreased with NADH-dependent substrates in Alzheimer's mice mitochondria.

Conclusion

From our investigations of Alzheimer's mouse model we was led to conclude that mitochondria functions were impaired in Alzheimer's mice, but knocking out the cyclophilin D protein improved the bioenergetic parameters. Our results showed that inhibitors of CypD protein (cyclosporine analogues) can be potential novell drug candidates in neurodegenerative diseases.

Methods

•**Mitochondrial isolation:** from 9 month old male mice with Percoll gradient centrifugation

•**Mitochondrial oxygen consumption measurement:** Oroboros High Resolution Oxygraph (Clark-electrode)

•**Mitochondrial ATP production linked enzyme assay measurement:** Jasco spectrophotometer 340 nm

•**Mitochondrial H₂O₂ production Amplex UltraRed fluorescence measurement:** PTI spectrofluorometer 571/585 nm

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