Treatment of APP_{SL} transgenic mice with an ALDH2 activator as a promising treatment option for Alzheimer's disease

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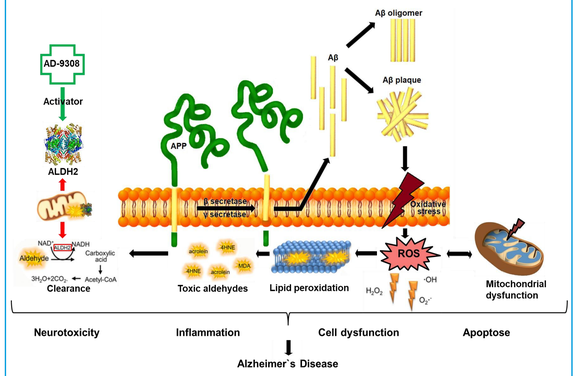
BACKGROUND

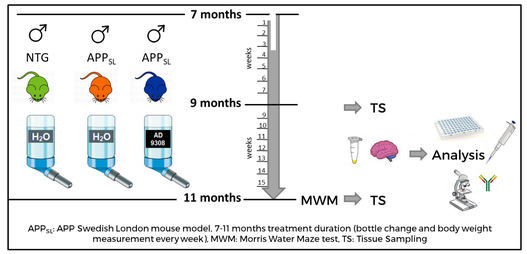
Alzheimer's disease (AD) is a severe neurodegenerative disorder. Progressive loss of mitochondrial function or defects in mitochondrial metabolism in the disease can lead to the generation of reactive oxygen species resulting in oxidation of membrane lipids and accumulation of toxic aldehydes in the brain and blood.



A mechanism for rapid clearance of these highly diffusible and harmful aldehydes is crucial to protect cells / tissues from damage. ALDH2 is located in the mitochondrial matrix and is a major enzyme involved in the clearance of reactive aldehydes. AD-9308 is a prodrug of a potent and selective activator (AD-5591) of ALDH2. The parent compound and active metabolite, AD-5591, has been found to promote ALDH2 activity in the oxidation of acetaldehyde, 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA) and propionaldehyde to the corresponding acid.

MATERIALS and METHODS

Male transgenic and non-transgenic littermates received either an ALDH2 activator AD-9308 or vehicle via drinking water over the time period of 4 months. Animals were housed in the AAALAC-accredited animal facility of QPS Austria and all tests were approved by the local government.



APP_{SL}: APP Swedish London mouse model, 7-11 months treatment duration (bottle change and body weight measurement every week), MWM: Morris Water Maze test, TS: Tissue Sampling

RESULTS

Cognitive improvements in the MWM test

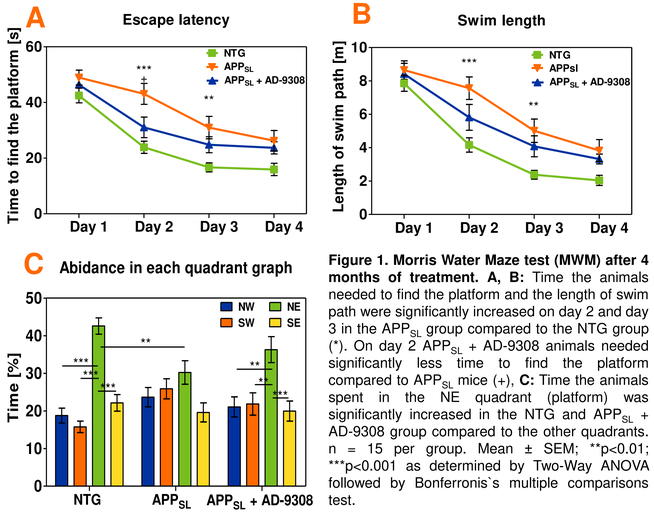


Figure 1. Morris Water Maze test (MWM) after 4 months of treatment. A, B: Time the animals needed to find the platform and the length of swim path were significantly increased on day 2 and day 3 in the APP_{SL} group compared to the NTG group (*). On day 2 APP_{SL} + AD-9308 animals needed significantly less time to find the platform compared to APP_{SL} mice (+), **C:** Time the animals spent in the NE quadrant (platform) was significantly increased in the NTG and APP_{SL} + AD-9308 group compared to the other quadrants. n = 15 per group. Mean ± SEM; **p<0.01; ***p<0.001 as determined by Two-Way ANOVA followed by Bonferronis`s multiple comparisons test.

RESULTS

Histologically measured changes in neuroinflammation & amyloid beta

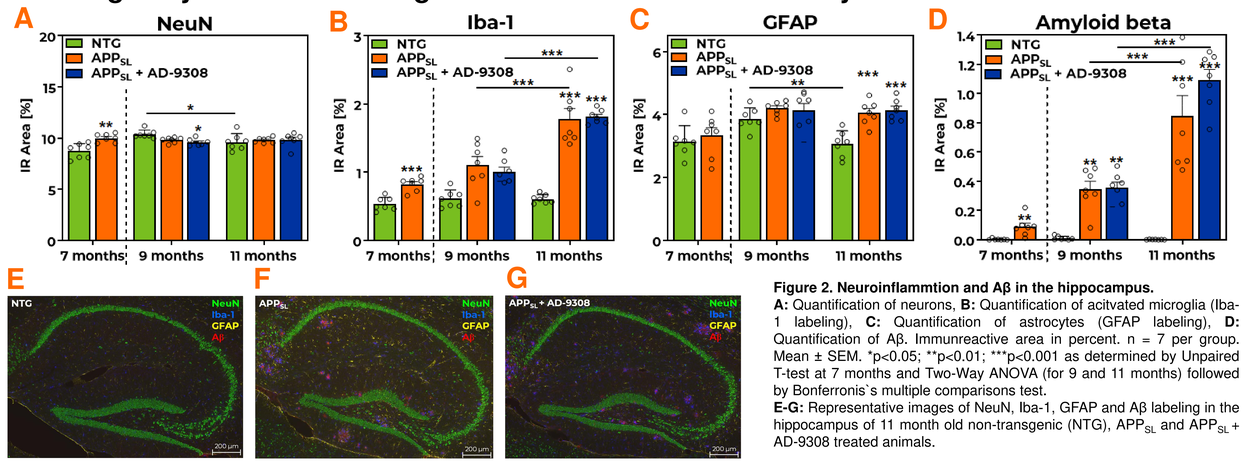


Figure 2. Neuroinflammtion and Aβ in the hippocampus.
A: Quantification of neurons, **B:** Quantification of acitvated microglia (Iba-1 labeling), **C:** Quantification of astrocytes (GFAP labeling), **D:** Quantification of Aβ. Immunreactive area in percent. n = 7 per group. Mean ± SEM. *p<0.05; **p<0.01; ***p<0.001 as determined by Unpaired T-test at 7 months and Two-Way ANOVA (for 9 and 11 months) followed by Bonferronis`s multiple comparisons test.
E-G: Representative images of NeuN, Iba-1, GFAP and Aβ labeling in the hippocampus of 11 month old non-transgenic (NTG), APP_{SL} and APP_{SL} + AD-9308 treated animals.

Biochemically changed metabolites

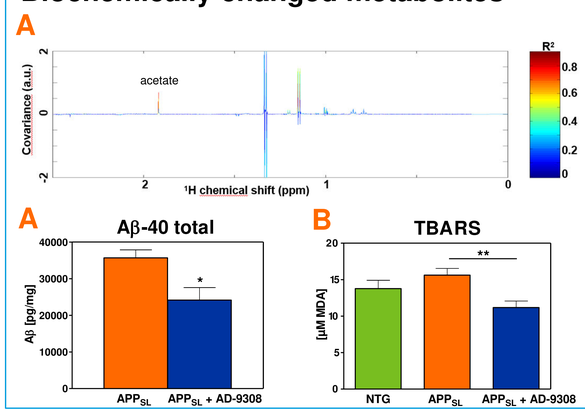


Figure 3. NMR metabolic profiling.
A: Reduced NMR spectra reveal altered metabolites in normalized serum samples. 1: acetate. Positive covariance corresponds to increased metabolite levels in APP_{SL} + AD-9308 compared to APP_{SL} mice after 4 months of treatment. Predictivity is represented by R2. **B:** Quantification of acetate levels in serum samples (n = 7) of APP_{SL} + AD-9308 mice compared to APP_{SL} mice. Unpaired t-test. Mean ± SEM. **p< 0.01.

Figure 4. Quantification of Aβ-40 and Thiobarbituric acid reactive substances (TBARS).
A: Aβ-40 quantification in the cortex of 11 month old mice. n = 6 per group. Mean ± SEM. *p<0.05 as determined by Unpaired T-test.
B: Quantification of malondialdehyde in serum samples of 11 month old mice. n = 13 per group. Mean ± SEM. **p<0.01 as determined by One-Way ANOVA followed by Tukey`s multiple comparisons test.

SUMMARY and CONCLUSION

The MWM test revealed a significant improvement of spatial learning in ALDH2 activator-treated animals compared to vehicle treated animals. AD-9308 did not reduce neuroinflammation in the brain but Aβ-40 and MDA levels were significantly decreased. Additionally, acetate levels were increased in AD-9308 treated animals compared to the control group. Further analysis has to be performed to better understand the pharmacological effect of the compound. Our results demonstrate that increasing the detoxification activity of ALDH2 is a promising approach to target AD.

For more information about the model please visit: www.qpsneuro.com
or send us an e-mail: office-austria@qps.com