An M1/sigma-1 receptor agonist prevents cognitive deficits, reduces amyloid plaques and neuroinflammation in a transgenic rat model of Alzheimer's amyloid pathology.

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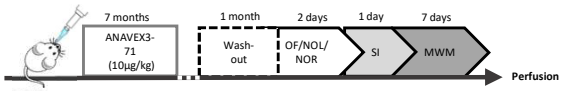
Background

- Acetylcholinesterase inhibitors represent four out of six drugs for treating Alzheimer's disease (AD), with time-limited efficacy likely due to the progressive loss of cholinergic neurons.
- The selective allosteric M1 muscarinic and sigma-1 receptor agonist ANAVEX3-71 (aka AF710B) [1] takes advantage of the fact that acetylcholine postsynaptic M1 muscarinic brain receptor levels remain unchanged in AD.
- ANAVEX3-71 treatment attenuated AD hallmarks in McGill-R-Thy1-APP transgenic rats when administered at advanced stages of the AD-like pathology [2]. However, AD therapy in humans has a greater likelihood of success if applied early in the disease prior to extensive brain damage arises.

For this reason, we tested whether ANAVEX3-71 administration during early amyloid pathology stages could prevent cognitive impairment, plaque deposition and neuroinflammation.

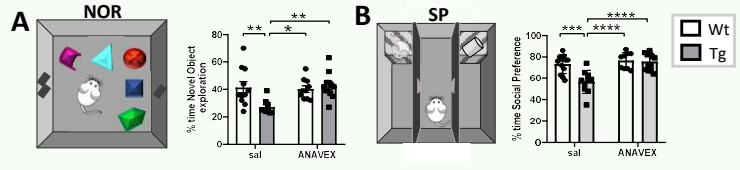
Methods

- ANAVEX3-71 (10 µg/kg) or saline was administrated daily p.o. in pre-plaque McGill-R-Thy1-APP (n=22) and wild-type (n=22) divided into four groups, for seven months.
- After one month of drug interruption, behavioural tests were performed: Novel Object Recognition (NOR), Morris Water Maze (MWM) and Social Preference (SP).
- Brains were extracted, fixed and analyzed by histochemistry and immunohistochemistry.



Statistical analysis: for 4-group analysis, 2x2 ANOVA followed by Tukey's multiple comparisons test. For 2-group analysis Mann Whitney test (data normality violated). Data are presented as mean ± SEM. *P ≤ 0.05; **P ≤ 0.01; ***P ≤ 0.001; ****P ≤ 0.0001.

Results

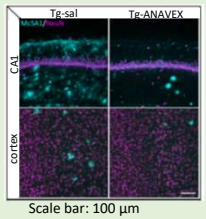


ANAVEX3-71 prevents McGill-APP rats from cognitive decline.

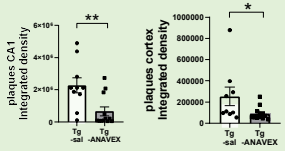
A. In the NOR, Tg-sal explored the novel object significantly less then wt-sal (P ≤ 0.01). The impairment was rescued in Tg-ANAVEX (P ≤ 0.01).

B. In the SP, Tg-sal rats showed less interaction time with a "stranger rat" than the wt-sal (P ≤ 0.001). This deficit was recovered in the Tg-ANAVEX (P ≤ 0.0001).

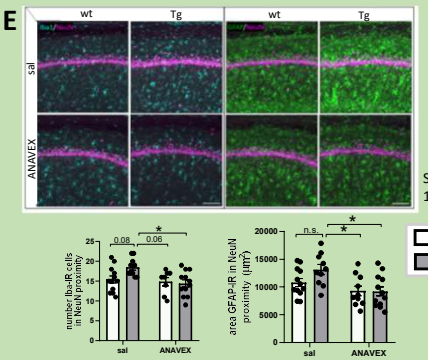
C. During the acquisition phase of the MWM, the rats showed significant differences in learning in the last three days. Averaging escape latencies from day 3 to 5, the Tg-sal required more time to find the hidden platform than wt-sal (P ≤ 0.01). Conversely, Tg-ANAVEX performed significantly better than the Tg-sal (P ≤ 0.05).



ANAVEX3-71 prevents McGill-APP rats from increasing cortical and hippocampal extracellular Aβ deposition.



D. McSA1-immunoreactive (IR) plaques intensity of Tg-ANAVEX was significantly lower in CA1 (P ≤ 0.01) and the cortex (P ≤ 0.05) compared to the Tg-sal.



ANAVEX3-71 reduces microglia and astrocytes recruitment towards Aβ-burdened neurons in the hippocampus

E. Iba1-IR and GFAP-IR cells in Tg-ANAVEX were significantly less recruited in the proximity of the CA1 neurons compared to the Tg-sal (P ≤ 0.05, for both).

References

[1] Fisher et al., 2016; Neurodegenerative Diseases. DOI:10.1159/000440864
[2] Hall et al., 2018; Alzheimer's & Dementia. DOI:10.1016/j.jalz.2017.11.009 .

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Conclusion

The long-lasting effect of ANAVEX3-71 in preventing cognitive decline of McGill-R-Thy1-APP rats, even after a wash-out period would suggest some preventative, disease-modifying, properties of the compound over the AD-like amyloid pathology.