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EFFECTS OF THE SIGMA-2 RECEPTOR ANTAGONIST ADV462 ON COGNITIVE AND MOTIVATIONAL IMPAIRMENT IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

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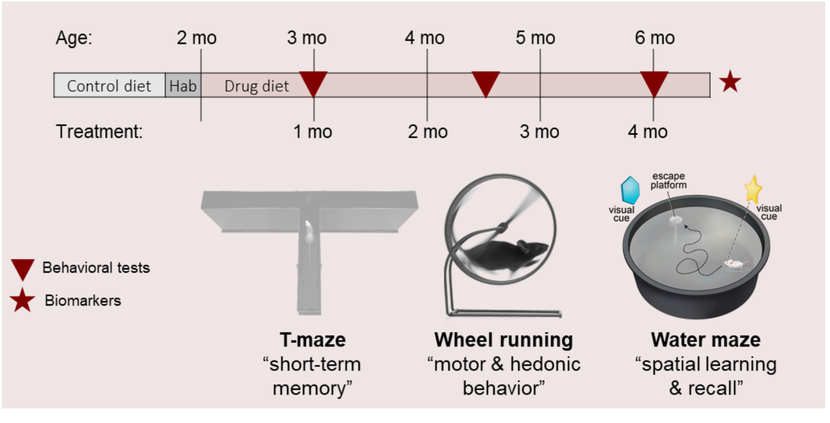
PURPOSE

This study aims to determine whether ADV462, an orally active and selective sigma-2 receptor antagonist (S2R), can mitigate cognitive and motivational impairment in the 5xFAD mouse model, a well-recognized animal model of Alzheimer's disease (AD).

METHODS

- A drug discovery program was undertaken to identify ADV462, a novel selective, orally active, S2R antagonist (Ki = 13 and >1000 nM for S2R and S1R, respectively).
- 5XFAD/B6SJL-Tg6799 (5XFAD) male and female mice, and age-matched non transgenic littermates were used. Breeder stocks were obtained from The Jackson Laboratory (Bar Harbor, ME) and their offspring were raised and maintained in the PCB Animal Facilities. Medicalized diet was prepared in form of pellets by Ssniff Spezialdiäten GmbH consisting of AIN-93M rodent maintenance diet containing ADV462 (200 ppm of food).
- 5xFAD mice were treated with ADV462 or a control diet from 2 to 7 months of age. Mice were randomly assigned into three groups (n=14 males and 12 females, per group):
  - I) WT Control: fed with standard diet
  - II) 5xFAD mice fed with standard diet
  - III) 5xFAD mice fed with ADV462

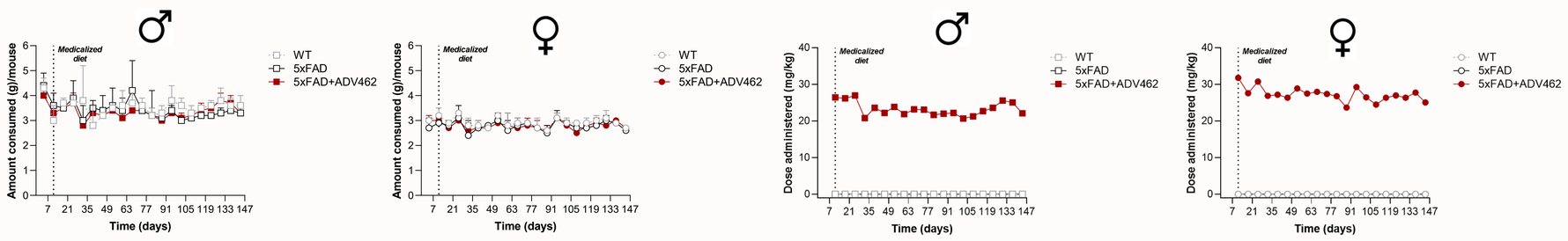
- Cognitive and motivational functions were evaluated using the T-maze, Wheel running, and Morris water maze tests, and the neuroprotective effects of ADV462 were determined based on these behavioral outcomes. Brain and plasma were collected at the end of the experiment for Biomarker analysis. Plasma and brain concentrations of ADV462 were assessed by UPLC-MS/MS.



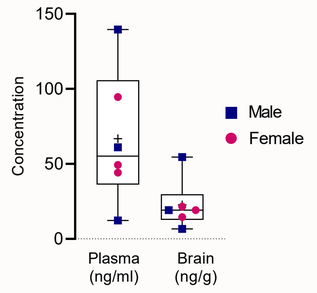
- The **T-maze** apparatus was a plastic maze with two choice arms (shaped like a "T"). In the training trial, one arm was closed (novel) and mouse was allowed to explore for 10 min only one arm (familiar). After intertrial intervals of 15 min, the mouse was placed back on the T-maze and allowed to freely explore both the familiar and novel arm for 5 min.
- The **Wheel running** was a Vertical Wireless Running Wheel by Med Associated. The revolutions spent running on the wheel were recorded. Each mouse was placed for 8 hours in a cage with free access to the wheel.
- The **Morris water maze** test was carried out in a circular pool (150 cm diameter, 50 cm depth), filled with water and stained using non-toxic white tempera. A platform was submerged in the pool, 1-2 cm below the water level, in the middle of the northeast quadrant, and the animals were allowed to swim freely to find it, during four consecutive trials, for a total of 12 days. The time to reach the platform (latency to target, seconds) were recorded.

RESULTS

ADV462 dose and plasma/brain levels

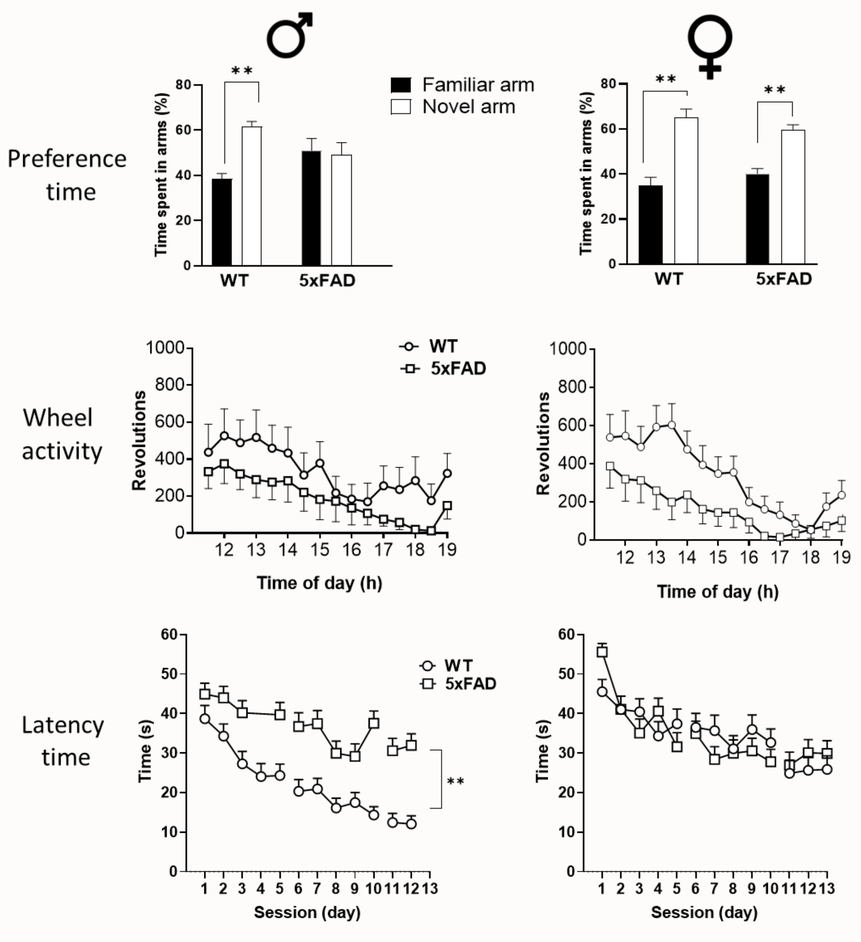


ADV462 was well tolerated after oral administration through the diet during the whole study. There was no change in the amount consumed in any of the experimental groups of mice. The drug dose supplied through the formulated diet remained stable. The average dose (mean from day 7 to day 147) of ADV462 was 23 and 27 mg/kg for male and female mice, respectively.



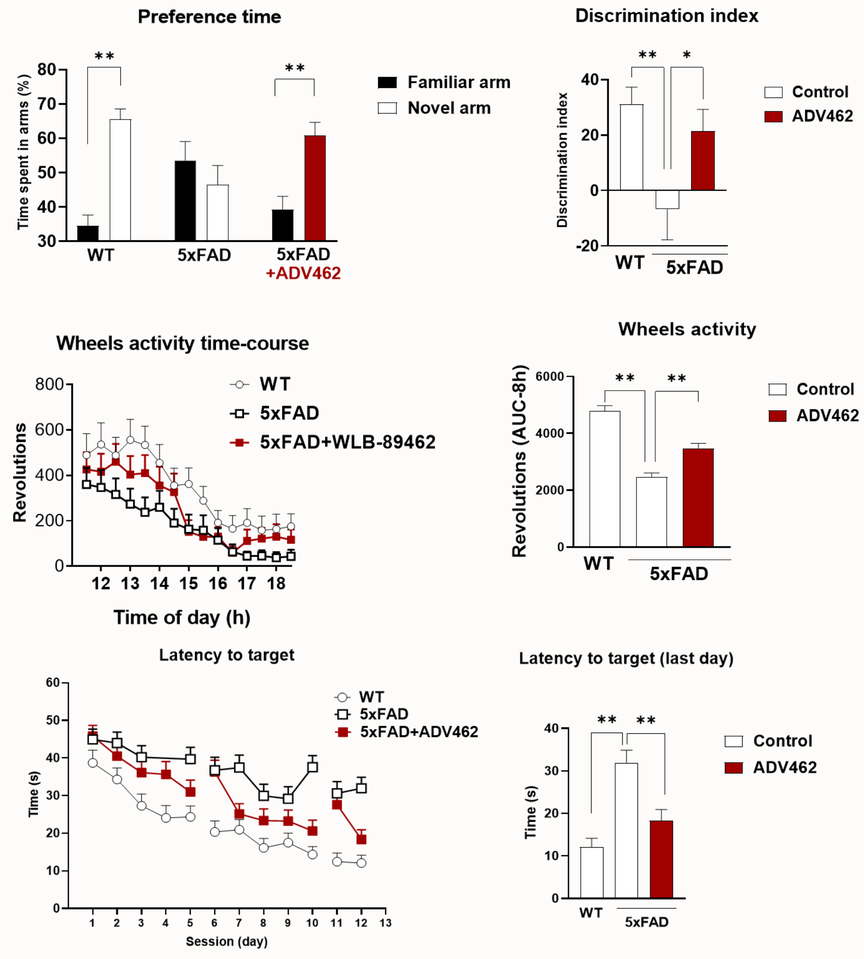
Plasma and brain concentrations of ADV462 determined at the end of the study were 71 ng/ml and 27 ng/g for males and 63 ng/ml and 19 ng/g for females.

Male vs Female



There are sex-related differences in the studied parameters. Male but not female 5xFAD animals showed short term (T-maze) and spatial memory (MWM) impairment. Wheel activity was altered in both sexes (** P<0.01).

ADV462 efficacy



The administration of ADV462 significantly reversed wheel activity, short term memory (T-maze) and spatial memory (MWM) deficits in 5xFAD animals (** P<0.01).

CONCLUSION

ADV462, an orally active and selective sigma-2 receptor antagonist, has demonstrated neuroprotective properties in the 5xFAD mouse model of AD, confirming that sigma-2 modulation could be a promising therapeutic approach for the treatment of neurodegenerative diseases, especially AD.