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POSTER COMMUNICATION – ABSTRACT

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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The sigma-2 receptor (σ2R) has been investigated in the context of cancer treatment and imaging. However, a growing interest in the σ2R as an innovative treatment in neurological diseases, particularly in Alzheimer's disease (AD) is evidenced. In the present study we evaluated the neuroprotective effects of a chronic administration of ADV462, a novel selective, orally active, σ2R antagonist (Ki = 13 and >1000 nM for σ2R and σ1R, respectively) in the 5xFAD mouse model of AD.

Male and female 5xFAD mice were treated with medicalized diet containing ADV462 (200 mg/kg feed; theoretically equivalent to a daily dose of 30 mg/kg) or vehicle (standard control diet). A control group with the same genetic background and fed with standard diet was run in parallel. Based on the daily food intake of the mice, the actual mean daily dose of ADV462 was determined to be approximately 25 mg/kg. Treatments began at 2 months of age and ended at approximately 7 months. Short-term memory (T-maze, at 1 month of treatment), motivation for physical activity (wheel running test, at 2.5 months of treatment) and spatial memory (Morris water maze, MWM) test, at 4 months of treatment) were assessed. Behavioral results showed different motivational and cognitive deficits in 5xFAD mice depending on sex and task compared with control animals. Short-term memory assessed by T-maze, and spatial memory assessed by MWM test, was impaired in male 5xFAD mice, but not in females. Motivation for physical activity assessed by wheel running was impaired in 5xFAD animals of both sexes.

ADV462 was well tolerated after oral administration through the diet during the whole study. Plasma and brain concentrations 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.

Cognitive and motivational impairment was prevented by ADV462. Specifically, ADV462 was effective in preventing short-term memory loss ($p<0.05$; discrimination index) and improved spatial memory in the MWM test ($p<0.01$; latency to target) in 5xFAD males. ADV462 also partially restored motivation for physical activity in both males and females ($p<0.05$; revolutions, AUC0-8 h).

In conclusion, ADV462 has potential neuroprotective properties reducing cognitive and motivational impairment in 5xFAD mice, and may be beneficial in the treatment of neurodegenerative disorders, particularly AD.