Passive immunization with the anti-Aβ oligomer antibody ACU-3B3 improves behavioral deficits in $hAPP_{SL}$ transgenic mice

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ABSTRACT

Recent clinical trials using antibodies directed against monomeric or fibrillar forms of Aβ have brought disappointing results. Based on the reported synaptotoxicity of soluble Aβ oligomers, we postulated that an antibody with selectivity for soluble Aβ oligomers would yield more encouraging data. ACU-3B3, the murine precursor to the clinical candidate ACU-193, displays selective affinity for soluble Aβ oligomers and therefore has a different anti-Aβ profile than previously developed antibodies targeting monomeric or fibrillar Aβ. In a recent study, 9-10 month-old hAPPSL mice were administered ACU-3B3 (20 mg/kg) or vehicle intraperitoneally (i.p.) once a week for 4 weeks and their performance assessed in the Water Maze learning paradigm. hAPPSL mice demonstrated significant behavioral deficits (i.e., longer swim path, longer escape latencies and faster swim speed) that were significantly improved by treatment with ACU-3B3. In a second study, 5-7 month-old hAPPSL mice were used to assess the effects of ACU-3B3 treatment on open field activity, Y-maze spontaneous alternation and passive avoidance performance. After weekly treatment with ACU-3B3 (i.p., 20 mg/kg), open field activity in hAPPSL mice fell to a level comparable to wild-type mouse controls, particularly activity in the center of the arena. Hyperactivity in the Y-maze spontaneous alternation task was also significantly improved by the treatment. Finally, ACU-3B3 treatment tended to improve passive avoidance memory in hAPPSL mice. Thus, these studies indicate that subchronic treatment with ACU-3B3, an antibody with high selectivity for soluble oligomeric forms of Aβ versus monomeric and fibrillar Aβ improves a wide range of behavioral deficits in hAPPSL mice. Our data suggest that ACU-3B3 targets toxic species of Aβ responsible for behavioral deficits in hAPPSL mice and such antibody selectivity may translate to clinical benefits for Alzheimer's disease.

METHODS

This study complied with all applicable sections of the current version of the Final Rules of the Animal Welfare Act Regulations (9 CFR) and the Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, 2010., and was approved by the IACUC of Stanford University (APLAC 18466). All animals were born in the BFNL animal facility and were housed in the facility throughout the study. Animals were housed at a standard temperature (22 ± 1°C), in a reverse-cycle light-controlled environment with ad libitum access to food and water.

Group	N	IP Dose (mg/kg)	Sex	Average Age At Start
APP+, vehicle	15	0	M	P164
APP+, 3B3 20mg/kg	15	20	M	P158
APP+, 3B3 30mg/kg	14	30	M	P163
WT, vehicle	14	0	M	P167

Activity Chamber

The test was conducted in a square arena, 43.2 x 43.2 cm, mounted with three planes of infrared detectors, within a specially designed sound attenuating chamber. Each was individually placed in the center of the testing arena and allowed to move freely for a 15-minute session. Distance moved and time spent in pre-defined zones of the arena, average velocity, resting time, jumping movement, and ambulatory movement are recorded.

Spontaneous Alternation Y-maze

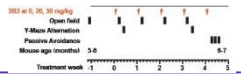
The test was conducted in a solid white plastic y-maze with three arms separated by 120°: two equal arms (15.24 cm x 12.7 cm x 7.62 cm) and one longer arm (20.32 cm x 12.7 cm x 7.62 cm). Each mouse was allowed to explore the maze for 5 minutes. An arm entry was defined as all four limbs of the subject into the arm. After testing, the entries are scored for the number of alternations, defined as any combination of 3 unique arms (e.g. "ABC", "BAC", but not "CAC"). The number of possible alternations is also defined and a percent alternation rate is calculated as: Number of alternations / Total number of possible alternations*100.

Passive Avoidance

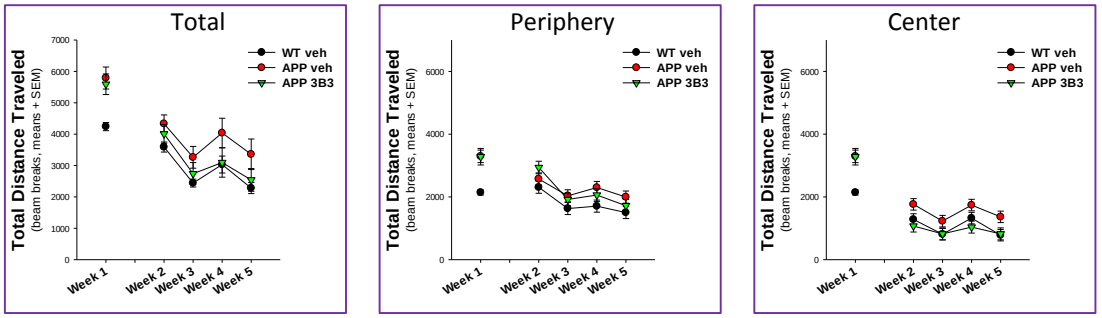
For step-through passive avoidance, GIMINI TM system from San Diego instruments is used. This automated system contains two compartments that are separated by a guillotine door (gate). Both compartments have a grid floor capable of delivering electrical shock. Usually one compartment is lit with bright white light and the second compartment is dark.

On the first day of testing (habituation), the mouse is placed in the lit compartment (start compartment). After 30 seconds of acclimation, the gate is opened and the mouse is free to explore both compartments. Twenty-four hours later (acquisition), the mouse is placed in the start compartment and after 30 seconds of acclimation the guillotine door is lifted. Three seconds after the door is closed a footshock (0.5 mA for 2 seconds) is delivered. The mouse remains in dark chamber for an additional 30 seconds. On testing day(s), the mouse is returned to the start compartment and after 5 seconds acclimation, the door is opened. When the mouse enters the dark compartment, the gate closes, and the latency to pass the gate, an indicator of learning and memory, is recorded. The latency to enter the dark compartment is recorded during each session.

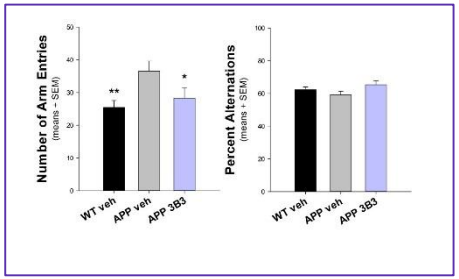
Treatment/Testing design



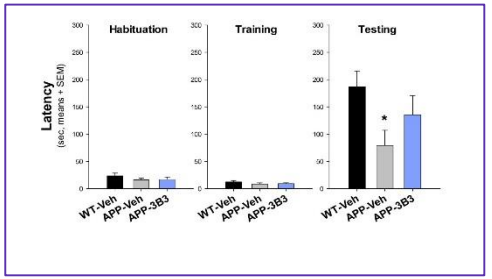
Open field Activity



Y-Maze Spontaneous Alternation



Passive Avoidance



CONCLUSION

The present study shows a trend of enhanced performance in the APP+ 3B3 20 mg/kg group when compared to APP+ Vehicle. Hyper-activity displayed in APP+ Vehicle mice in the Activity Chamber, exhibited by increased distance moved, and in the Y-Maze, exhibited by increased number of arm entries, are partially recovered in the 3B3 20 mg/kg group. In both tests, the activity levels of APP+ mice treated with 3B3 20 mg/kg are very similar to those of WT Vehicle mice. In the Passive Avoidance test, 3B3 20mg/kg tends to improve learning and memory in APP+ mice, but this improvement is not significant. Taken together, the present study suggests that treatment group 3B3 20 mg/kg may be effective in improving the symptoms associated with the disease.