Soluble Aβ-oligomer–selective Antibody ACU-3B3 Reduces Amyloid Pathology and Improves Multiple Behavioral Domains in a Mouse Model of Alzheimer's Disease

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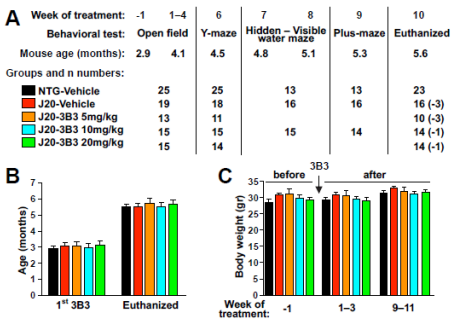
Abstract

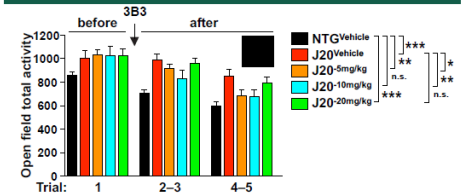
Considerable evidence suggests that amyloid-beta (Aβ) and tau contribute to neuronal and cognitive abnormalities in Alzheimer's disease. However, recent failed clinical trials targeting Aβ raised conceptual concerns. Because Aβ exists in multiple assembly states in vivo, we tested the therapeutic effects of the highly soluble Aβ-oligomer selective antibody ACU-3B3, the murine precursor to the clinical candidate antibody ACU-193, which has a different anti-Aβ profile than previously developed antibodies targeting monomeric or fibrillar Aβ. hAPPJ20 mice (mixed gender, n=62) received weekly intraperitoneal treatments with vehicle (PBS) or ACU-3B3 at 5, 10 or 20 mg/kg. Treatment began at the earliest stages of amyloid deposition (3–5 months) and continued for 10 weeks until mice were 5–7 months old. During the 10-week treatment period, mice were assessed in multiple behavioral domains, including locomotor activity, emotional behaviors, and cognitive functions. Across all experimental groups, mouse body weights remained stable during the 10-week period, indicating that ACU-3B3 was well tolerated at all doses. ACU-3B3 treatment reduced the hyperactivity phenotype of hAPPJ20 mice and normalized their locomotor activity to near non-transgenic levels in the open field and Y-maze paradigms. Emotional alterations of hAPPJ20 mice in the elevated plus-maze were also normalized by ACU-3B3 treatment. Cognitive performance was assessed in the context-dependent habituation test and in the visible and hidden versions of the Morris water maze. ACU-3B3 treatment enhanced cognitive performance in the novel environment habituation test (context learning) and in the visible platform water maze training (non-spatial learning), but not in the hidden version of the test (spatial learning). After 10 weeks of treatment, mouse brains were collected for pathological analyses. ACU-3B3 treatment reduced amyloid deposits in the hippocampus and cortex in a dose-dependent manner. Our data indicate that the ACU-3B3 targets an Aβ assembly state that is responsible for in vivo amyloid formation and behavioral deficits in hAPPJ20 mice and clinical benefits may be achievable with second generation passive immunization approaches.

Experimental Design



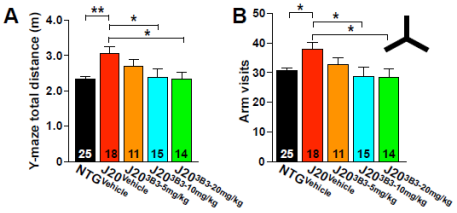
hAPPJ20 mice (J20) were weekly injected IP with 5, 10, and 20 mg/kg of mouse anti-Aβ-oligomer antibody (ACU-3B3) or vehicle (PBS) for 10 weeks. Non-transgenic (NTG) mice received vehicle injections. A) Locomotor activity, emotion-like behaviors and cognitive functions were assessed in the open field, y-maze, and elevated plus-maze tests during the 10-week treatment period. B) Age of the experimental groups at the first ACU-3B3 or vehicle injection and at completion of the study. C) ACU-3B3 treatment did not alter mouse body weight during the 10-week treatment period.

ACU-3B3 Treatment Reduces Habituation Deficits in J20 Mice



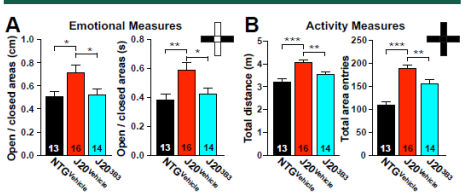
Untreated J20 mice (n = 62 naive J20 mice) were first tested in the open field (trial 1) and randomly assigned to vehicle or ACU-3B3 experimental groups. Thereafter mice were monitored for open field activity 24h after each weekly injection. Open field activity data are presented as average of trials 2-3 (middle bars) or 4-5 (right bars). One-way ANOVA and Bonferroni's multiple comparison tests for open field trials 2–5 (after ACU-3B3 treatment) confirmed that ACU-3B3 treatment reduced the hyperactivity phenotype in J20 mice at 5 and 10 mg/kg. *p<0.05, **p<0.01, and ***p<0.001 by one-way ANOVA and Bonferroni test.

ACU-3B3 Treatment Prevents the Hyperactivity Phenotype in J20 Mice



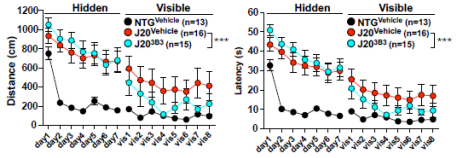
After 6 weeks of ACU-3B3 treatment, total locomotor activity (A) and arm visits (B) were assessed in the Y-maze. Spontaneous alternation was not altered in J20 mice (data not shown). However, ACU-3B3 treatment significantly prevented the hyperactive phenotype of hAPPJ20 mice at 10 and 20 mg/kg. Bars represent mean + SEM. Numbers in bars are number of mice. *p<0.05, and **p<0.01 by one-way ANOVA and Bonferroni test .

ACU-3B3 Treatment Reduces Emotional Deficits in J20 Mice



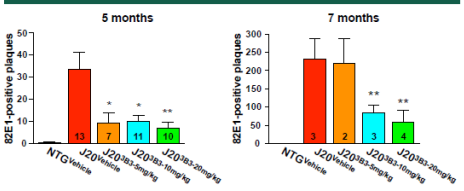
After 9 weeks of ACU-3B3-10mg/kg treatment, mice were tested in the elevated plus maze to assess their emotional response to an anxiogenic environment. A) The percent time spent in open arms was significantly higher in J20-Vehicle mice, a phenotype that was prevented by ACU-3B310mg/kg treatment (J20-3B3 mice) (left, distance; right, time) (B). ACU-3B3-10mg/kg treatment also reduced the hyperactive phenotype in the elevated plus maze. Bars represent mean + SEM. Numbers in bars are number of mice. *p<0.05, **p<0.01, and ***p<0.001 by one-way ANOVA and Bonferroni test .

ACU-3B3 Treatment Reduces Visible Platform Water Maze Training Deficits in J20 Mice



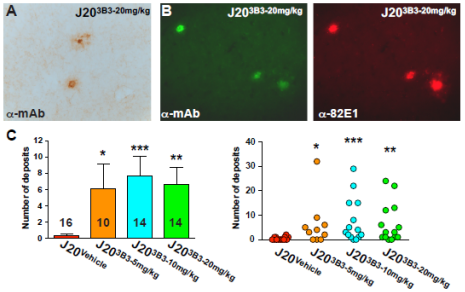
After 7 and 8 weeks of ACU-3B3-10mg/kg treatment, mice were tested in the hidden and visible versions of the water maze (left, distance; right, latency). ACU-3B3-10mg/kg treatment did not improve performance in the hidden version of the test (spatial learning), but improved performance in the visible version of the test (non-spatial learning).

ACU-3B3 Treatment Reduces Amyloid Plaques in J20 Mice



After 10 weeks of treatment, mouse brains were collected for pathological analyses. ACU-3B3 treatment reduced 82E1-positive amyloid deposits in the hippocampus and cortex in a dose-dependent manner at 5 (left) and 7 (right) months of age in J20 mice. Bars represent mean + SEM. Numbers in bars are number of mice.*p<0.05, and **p<0.01by one-way ANOVA and Bonferroni test .

Detection of 3B3 in Brain Tissue After IP Treatment



After 10 weeks of treatment, mouse brains were collected for pathological analyses. ACU-3B3 antibodies were detected in the brains of ACU-3B3-J20-treated mice by anti-mouse secondary antibodies after 10 weeks of ACU-3B3 treatment. ACU-3B3 antibodies colocalized with 82E1-positive amyloid deposits in the hippocampus and cortex. Bars represent mean + SEM. Numbers in bars are number of mice.*p<0.05, and **p<0.01by one-way ANOVA and Bonferroni test .