Background: After age, the second largest risk factor for Alzheimer's disease (AD) is apolipoprotein E (APOE) genotype, where APOE4 is associated with lower apoE protein levels, more severe brain pathology, enhanced inflammation and disease. Small peptides corresponding to the receptor-binding region of apoE mimic the anti-inflammatory activity of the apoE holoprotein. These apoE mimetics greatly improve behavioral outcomes and neuronal survival in head trauma models that display AD pathology and neuronal loss. Objective: To determine whether apoE mimetics change behavior, inflammation and pathology in CVND-AD (SwDI-APP/NOS2(-/-)) transgenic mice. Methods: Starting at 9 months, apoE peptides were subcutaneously administered 3 times per week for 3 months followed by behavioral, histochemical and biochemical testing. Results: Treatment with apoE mimetics significantly improved behavior while decreasing the inflammatory cytokine IL-6, neurofibrillary tangle-like and amyloid plaque-like structures. Biochemical measures matched the visible pathological results. Conclusions: Treatment with apoE mimetics significantly improved behavior, reduced inflammation and reduced pathology in CVND-AD mice. These improvements are associated with apoE-mimetic-mediated increases in protein phosphatase 2A activity. Testing in additional AD models showed similar benefits, reinforcing this novel mechanism of action of apoE mimetics. These data suggest that the combination of anti-inflammatory and neuroprotective activities of apoE mimetics represents a new generation of potential therapeutics for AD.