Activation of the CB_2 receptor system reverses amyloid-induced memory deficiency

Abstract

Cannabinoid type 2 (CB_2) agonists are neuroprotective and appear to play modulatory roles in neurodegenerative processes in Alzheimer's disease. We have studied the effect of 1-((3-benzyl-3-methyl-2,3-dihydro-1-benzofuran-6-yl)carbonyl) piperidine (MDA7)—a novel, blood brain barrier-permeant, and highly selective CB_2 agonist that lacks psychoactivity—on ameliorating the neuroinflammatory process, synaptic dysfunction, and cognitive impairment induced by bilateral microinjection of amyloid-beta ($A\beta_{1–40}$) fibrils into the hippocampal CA1 area of rats. In rats injected with $A\beta_{1–40}$ fibrils, compared to the administration of intraperitoneal (i.p.) saline for 14 days, treatment with 15 mg/kg of MDA7 i.p. daily for 14 days (i) ameliorated the expression of CD11b (microglia marker; Fig. 1A) and GFAP (astrocyte marker; Fig. 1B), (ii) decreased the secretion of IL-1β (Fig. 1C), (iii) decreased the upsurge of CB_2 receptors (Fig. 1D), (iv) promoted Aβ clearance (Fig. 1E), and (v) restored synaptic plasticity (Fig. 1F), cognition and memory (Fig. 1G). The effects of MDA7 were abrogated by prior administration of a CB_2 antagonist AM630. The administration of AM630 alone did not result in any beneficial effect on Aβ-related pathology. Our findings suggest that MDA7 is an innovative therapeutic approach for the treatment of Alzheimer's disease.

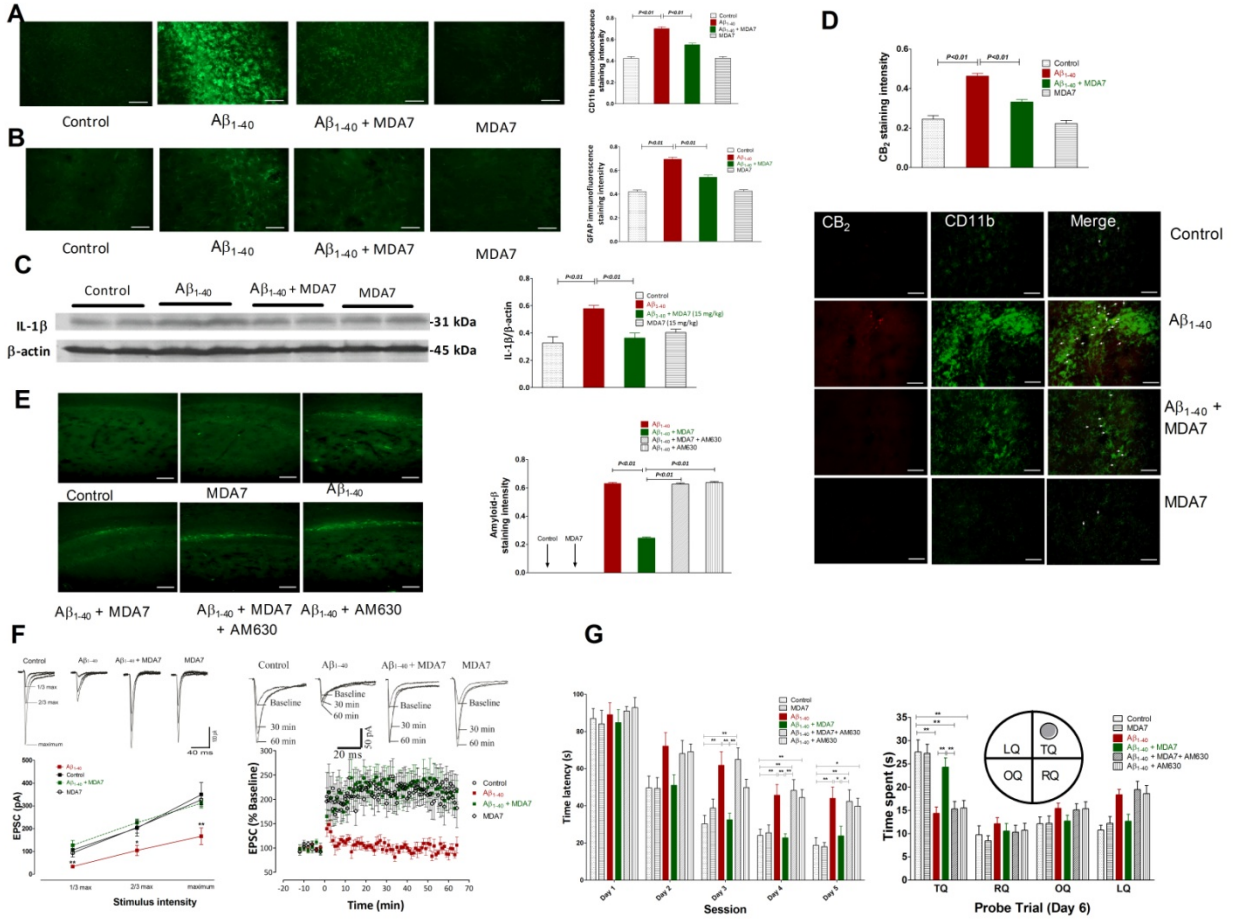

Fig. 1. *Administration of MDA7 clears β-amyloid and reverses deficits in Alzheimer's disease rat model. Statistical significance was determined by one-way ANOVA followed by Student-Newman-Keuls multiple range test. Data are shown as mean ± SEM (n = 8-10 per group). Scale bar = 40 µm. *P<0.05, **P<0.01.*