T-TYPE CALCIUM CHANNEL MODULATOR AD101 IMPROVES COGNITIVE FUNCTION IN ANIMAL MODELS OF MEMORY AND LEARNING IMPAIRMENT

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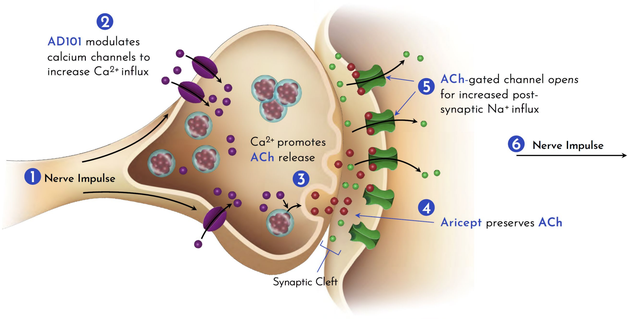
Background:

- AD101 is a novel synthetic compound in development as an orally administered treatment for Alzheimer's Disease (AD).
- AD101 was discovered through phenotypic screening and subsequently investigated in animal models for normal aging, memory and learning impairment and AD.
- AD101 stimulates the presynaptic release of acetylcholine in hippocampal neurons through CaV3.1 and CaV3.3 modulation (Figure 1).
- Furthermore, studies suggested additional effects on hallmarks of AD pathology.

Figure 1: Mechanism of action of AD101: AD101 enhances presynaptic Acetylcholine release in cholinergic hippocampal neurons. Added benef can be achieved through combination with cholinesterase inhibitors.



Objectives:

- Review the effects of AD101 on learning and memory function in animal models for normal aging, induced memory and learning impairment and Aβ and tau dependent models.
- Review combined effects of AD101 administration with available therapies such as cholinesterase inhibitors and memantine.

Methods:

- Review of previously published and unpublished nonclinical studies.

Results:

- Initial dose finding studies in rodents in investigated doses of AD101 ranging from 0.001 to 1.0 mg/kg produced an inverted U-shape in dose-response curves with optimum doses mostly between 0.01 and 0.1 mg/kg.
- Behavioral outcome measures used were the Novel Object Recognition (NOR), the Passive Avoidance (PA), the Radial Arm Maze (RM) and the Morris Water Maze Task (WWM).

Figure 2: Effect of AD101 on scopolamine-induced impairment in the PA task. After muscarinergic blockage via scopolamine administration AD101 significantly attenuated step-through latencies in the PA task.
p<0.01 compared with vehicle-treated control rats
** p<0.01 compared with scopolamine-treated rats given 1% CMC (vehicle)
CMC = carboxymethylcellulose

Figure 4: NOR performance after AD101 treatment and combination with memantine in normal mice. During retention control mice showed significant increases in the exploratory preference in the memantine (10 mg/kg) group and further increases in combination with AD101 (0.001 mg/kg).
p<0.01, compared with memantine (3 or 10 mg/kg)-treated mice
** p<0.01, compared with vehicle treated control mice

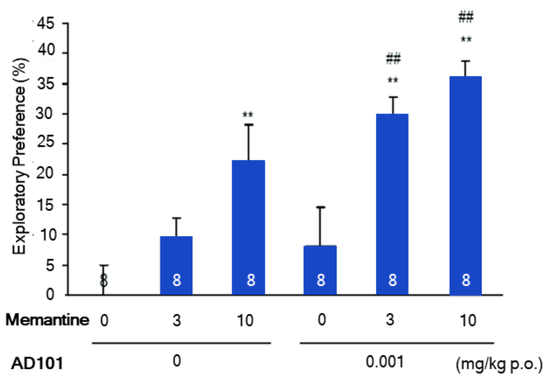


Figure 6: Effect of AD101 on methamphetamine-induced impairment in recognition memory in the NOR task. 7 days of exposure to methamphetamine induced impairments of recognition memory in the NOR. Those effects were attenuated by administration of 1µg/kg AD101.
** p<0.01, compared to saline-treated mice
p<0.01, compared to meth-treated mice

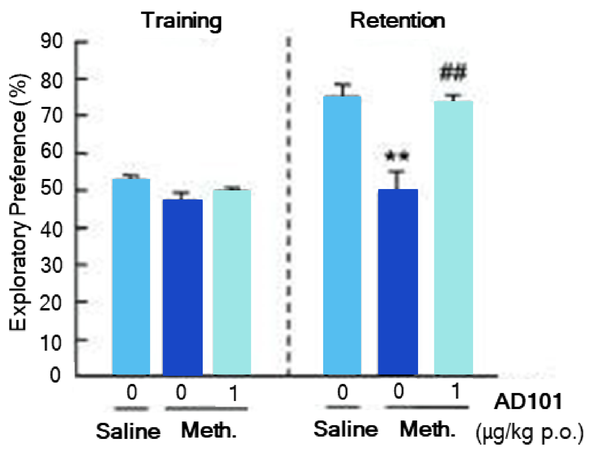


Figure 3: Effect of combination of AD101 with donepezil on scopolamine-induced impairment in the PA Task. A significant effect was seen in the 0.1 mg/kg donepezil group and the combination arms of 0.1 mg/kg and 0.1 mg/kg AD101 with donepezil which produced the highest effect sizes.
p<0.01 compared with vehicle-treated control rats
** p<0.01 compared with scopolamine-treated rats given 1% CMC (vehicle)
++ p<0.01 compared with scopolamine-treated rats given 0.01 mg/kg donepezil

Figure 5: Effect of AD101 on MK-801 induced impairment in PA task. Glutamatergic blockage via intraperitoneal administration of 0.2 mg/kg MK-801 (also known as Dizocilpine) significantly reduced step-through latency in the PA task. A single dose administration of 0.1 mg/kg but not of 1 mg/kg AD101 significantly ameliorated step-through latency.
# p<0.05, compared to vehicle-controlled rats
* p<0.05, compared to vehicle-controlled and MK-801-treated rats

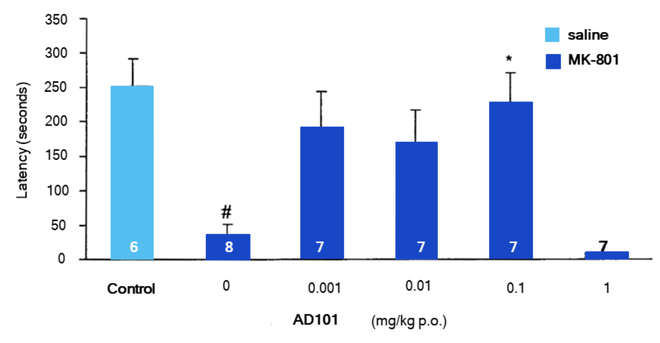
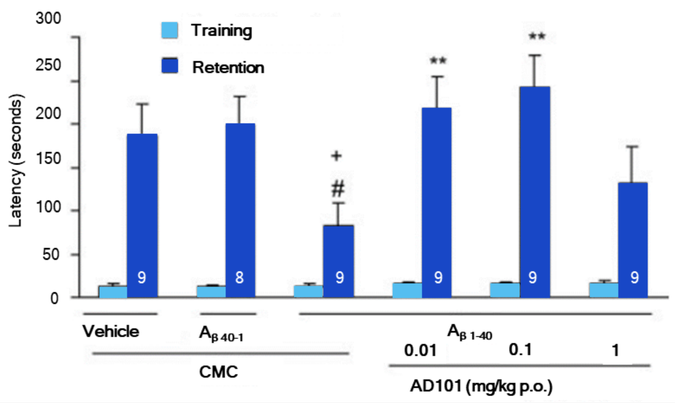


Figure 7: AD101 in memory impairment induced by Amyloid β_{1-40}. Intracerebroventricular infusion of $A\beta_{1-40}$ in rats produced deficits in the step-through latency in the PA task which were fully reversible by administration of 0.01 and 0.1 mg/kg AD101. Control rats were infused with vehicle or reverse control peptide Aβ40-1.
# p<0.05, compared with vehicle-infused control rats
+ p<0.05, compared with Aβ40-1-infused rats
** p<0.01, compared with Aβ1-40-infused rats given CMC



Results II:

- Beneficial effects of AD101 on various behavioral outcome measures were seen in normal animals (Figure 4), models of chemically-induced cognitive impairment (Figures 2, 3 and 5) and amyloid dependent models (Fig. 6).
- AD101 also attenuated cognitive impairment induced by lesioning of the Nucleus Basalis Magnocellularis (NBM) by ibotenic acid and intraventricular $A\beta_{25-35}$ injections (not shown).
- AD101 improved cognitive deficits in triple transgenic Mice (3xTG), an animal model for AD with age-dependent expression of Aβ-plaques, neurofibrillary tangles and neurobehavioral problems (Poster P190).
- Similar effects were seen in SAMP8 Mice a mouse strain that, via a spontaneous gene mutation, develops age-related deficits in learning and memory along with an accelerated accumulation of Aβ-like deposits in brain tissue (Poster P190).

Discussion:

- AD101 demonstrated beneficial effects on learning and memory function in animal models of normal aging, impaired learning and memory function and AD.
- These cumulative findings provide the rationale for further clinical use of AD101 in the symptomatic treatment of AD.

References:

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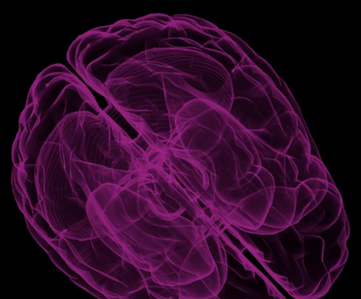

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