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Subchronic memantine administration on spatial learning, exploratory activity, and nest-building in an APP/PS1 mouse model of Alzheimer's disease

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ABSTRACT

Glutamate neurotoxicity has been proposed to be involved in Alzheimer pathogenesis, with clinical data supporting succesful treatment with the NMDA receptor antagonist memantine. In the present study, the effects of subchronic memantine administration were assessed on spatial and non-spatial learning as well as exploratory activity and nest-building in APP/PS1 mutant mice. Memantine (10 mg/kg, i.p.) was better than placebo during the reversal phase of left-right discrimination, though equivalent to saline for Morris water maze and passive avoidance learning. The drug had no effect on non-learned behaviors in elevated plus-maze exploration and nest-building. These results support a specific action of the NMDA receptor antagonist on behavioral flexibility in mutant mice with amyloid pathology.

1. Introduction

N-methyl-D-aspartate (NMDA) receptors are involved in synaptic plasticity and plays a crucial role in spatial learning, as in Morris water maze (Steele and Morris, 1999; Morris et al., 1986) and matching-to-place (Steele and Morris, 1999) paradigms. Because of its low- to moderate-affinity as a non-competitive antagonist of NMDA receptors (Szegedi et al., 2010), memantine appears all the more attractive in preventing excessive NMDA receptor activity without blocking synaptic transmission (Chen et al., 1998). Relative to placebo, memantine improved cognitive performances in patients with Alzheimer's disease (Bakchine and Loft, 2008; Ferris et al., 2009; Mecocci et al., 2009; Peskind et al., 2006; Pomara et al., 2007) and dementia with Lewy bodies (Emre et al., 2010), as well as activities of daily living in the former (Feldman et al., 2006). In addition, memantine is effective in treating neuropsychiatric symptoms of patients with Alzheimer and other dementias (Ballard and Corbett, 2010; Cummings et al., 2008; Maidment et al., 2008). The substance is thereby approved by the USA Food and Drug Administration and the European Medicines Agency as a modestly effective Alzheimer therapeutic agent (Cosman et al., 2007; Emre et al., 2008; McKeage, 2009; McShane et al., 2006; Mecocci et al., 2009; Parsons et al., 2007; Robinson and Keating, 2006; Schmitt et al., 2007; Thomas and Grossberg, 2009; Winblad et al., 2007), cost-effective in Canada (Gagnon et al., 2007), the USA (Weycker et al., 2007), and Spain (Antonanzas et al., 2006). It has been proposed in combination with other treatments, such as magnesium (Ozturk and Cillier, 2006). Memantine therapy is all the more relevant in that NMDA receptor subunits may predispose subjects to Alzheimer disease susceptibility (Liu et al., 2009) and targets Alzheimer-related neuropathology, as in reducing CSF levels of phosphorylated tau (Degerman Gunnarsson et al., 2007). However, the cognitive improvement in Alzheimer's disease is sometimes test-specific (Kubova et al., 2010; van Dyck et al., 2007), not correlated with event-related potentials (Kubova et al., 2010), and, in one study, not different from donepezil, the anticholinesterase agent (Modrego et al., 2010). Although generally safe (Ott et al., 2007), memantine may worsen neurologic symptoms and cause myoclonus (Papageorgiou et al., 2007) and visual hallucinations (Monastero et al., 2007).

Memantine treatment has been shown to be effective in transgenic mice with amyloid pathology, including spatial learning in the Morris water maze in three models: 3xTg (Martinez-Coria et al., 2010), APP_{751}SWE (Van Dam and De Deyn, 2006), and APPswe/PS1-A246E (Minkeviciene et al., 2004). Positive benefit was also

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obtained for object recognition memory in APP/PS1-L166P mutants (Scholtzova et al., 2008). But despite diminishing Aβ deposits, there was no improvement in contextual fear conditioning of APP_{695}SWE mice (Dong et al., 2008). Memantine also mitigated amyloid pathology by reducing membrane-bound APP in APP_{695}SWE mice (Unger et al., 2006), soluble $A\beta_{42}$ in APPswe + PS1ΔE9 mice (Alley et al., 2010), plaque burden in APP/PS1-L166P mice (Scholtzova et al., 2008), insoluble Aβ, Aβ dodecamers and fibrillar oligomers in 3xTg mice (Martinez-Coria et al., 2010), and secreted forms of APP and $A\beta_{40}$ in neuronal SK-N-SH cells (Ray et al., 2010). Likewise, memantine prevented $A\beta_{25\text{-}35}$-induced changes in rat hippocampus (Arif et al., 2009) as well as glutamate- (Cente et al., 2009) and $A\beta_{42}$-induced (Song et al., 2008) toxicity in rat cortical neuron cultures.

We assessed APPswe/PS1 mice expressing an *APP* transgene with the Swedish mutation on a chimeric human/murine 695-amino acid isoform bred with a *PS1*/A246E line, each driven by the endogenous *PrP* promoter (Borchelt et al., 1997), causing age-related increases in soluble and insoluble $A\beta_{42}$ and $A\beta_{40}$ (Marutle et al., 2002; Wang et al., 2003) with cognitive impairments during the reversal phase of left-right discrimination learning, passive avoidance learning, and nest-building (Filali et al., 2009), as well as the Morris maze (Liu et al., 2002; Puoliväli et al., 2002). We evaluated nest-building and the elevated plus-maze as non-learned tests relevant in the drug's mitigation of neuropsychiatric symptoms (Ballard and Corbett, 2010; Cummings et al., 2008; Maidment et al., 2008; Swanberg, 2007). We chose a dose of 10 mg/kg for three weeks, based on positive findings in other transgenics with 14.4 mg/kg s.c minipumps for 2 months (Van Dam and De Deyn, 2006) and 30 mg/kg in drinking water for 3 months (Martinez-Coria et al., 2010) or 3 weeks (Minkeviciene et al., 2004).

2. Materials and methods

2.1. Transgenic animals

Male transgenic mice bearing a chimeric human/mouse *APP* gene with the Swedish mutation combined with the A246E variant of the human *PS1* gene, strain B6C3-Tg(APP695)3Dbo Tg(PSEN1)5Dbo/J, were purchased from the Jackson Laboratory, Bar Harbor, ME, USA. The mice were first on a B6C3 background and backcrossed for at least 10 generations to C57BL/6J. Group-housed APPswe/PS1 transgenic and littermate wild-type mice ($N = 60$, 8 month-old) were separated into 3 groups: APP + saline 0.9%, $n = 20$, APP + memantine 10 mg/kg, $n = 20$, and wild-type + saline, $n = 20$). Memantine hydrochloride was purchased from Sigma–Aldrich (St-Louis, MO, USA) and injected i.p. in a volume of 5 cc/kg 3 times per week for 3 weeks in a schedule depicted in Fig. 1.

All mice had continuous access to food and water in a temperature-controlled room under natural lighting conditions with a 12/12 h light-dark cycle (lights on at 7:00) and their health regularly checked with modified SHIRPA primary screening (Rogers et al., 1997). The genotype status of all newborn pups was confirmed by DNA analysis of tail biopsies. Animals were tested by an experimenter blind to treatment during the light phase, following guidelines of the Canadian Council on Animal Care, with a protocol approved by the Animal Welfare Committee at the University of Laval.

2.2. Behavioral tests

Three AD-related behavioral functions were assessed: social behavior, exploratory activity, and spatial learning. The nesting test was given first, followed by elevated plus-maze, left-right discrimination learning, and passive avoidance learning. For the Morris water maze, a separate series were randomly assigned to the

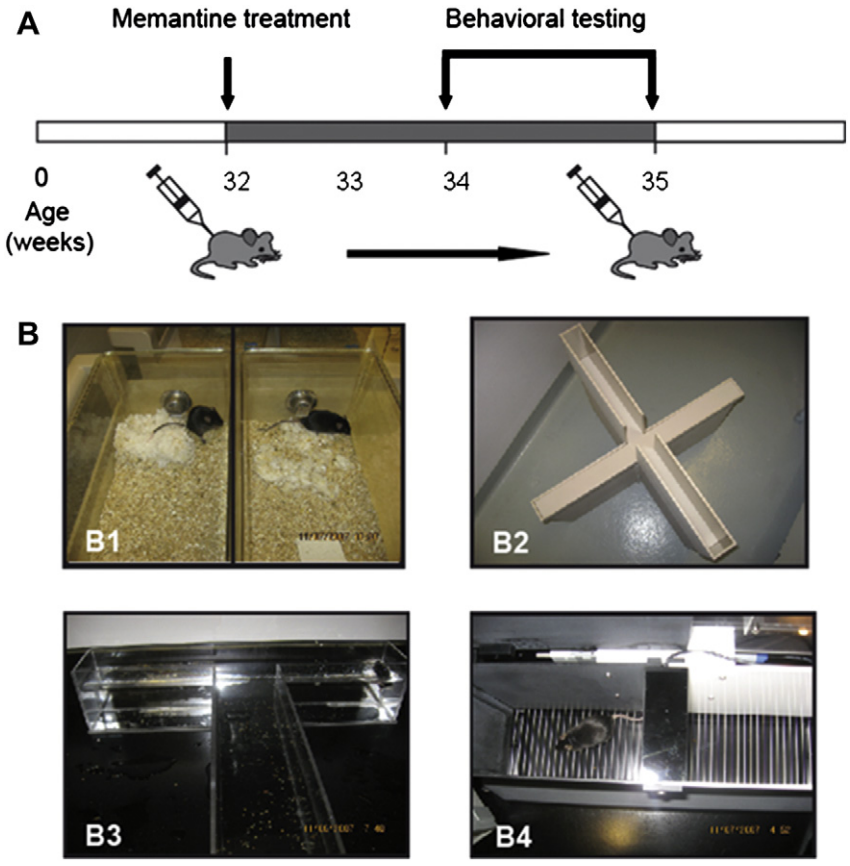

Fig. 1. Time line and behavioral tasks. A. Experimental time line. B1. Quality of nest construction was assessed. Left, perfect nest in wild-type mice. Right, no identifiable nest in APPswe/PS1 mice. B2. Elevated plus maze: the mice were tested for 3 min. B3. T-water maze used to test left-right spatial discrimination and learning flexibility. B4. Passive avoidance: the mice were trained to avoid the preferred dark compartment by pairing it with an aversive stimulus.