# Memantine Rescues Cholinergic Neurons from the Neurotoxic Effects of β-Amyloid (Aβ1-42)

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also reduced in memantine-treated media compared to control. These data suggest that memantine may affect APP processing and may potentially inhibit the accumulation of fibrillogenic Aβ peptides.

**Conclusions:** Further experiments are in progress to better understand the mechanism of memantine's effect on secretases.

## P.5.b.005 Memantine rescues cholinergic neurons from the neurotoxic effects of β-amyloid (Aβ1–42)

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**Background:** Memantine, a moderate affinity uncompetitive NMDA receptor antagonist, is approved for the treatment of Alzheimer's disease (AD).

**Objective(s):** The mechanisms by which memantine exerts its beneficial effects in AD are under investigation. Memantine has been shown to provide neuroprotection and improve learning and memory in several animal models. It has also been shown that therapeutic doses of memantine reduce the levels of amyloid precursor protein (APP), Aβ1–40 and Aβ1–42 peptides in human neuroblastoma cells and in the rat primary cortical neurons.

**Methods:** In this study, the neuroprotective effects of memantine were determined in rats with multiple unilateral Aβ1–42 lesions in the nucleus basalis magnocellularis (NBM) and parietal neocortex. The contralateral side of the brain served for control. Memantine (30 mg/kg/day) was given orally via drinking water starting 3 days prior to lesioning and continued for 10 postoperative days. For behavioural analysis open-field exploration, novel object recognition (attention) and one-trial step-through passive avoidance learning paradigms were applied starting the analysis 3 days after lesion. At the end of chronic memantine treatment (10 days after lesion) the animals were sacrificed for histological examination. The impact of amyloid peptide toxication on cholinergic cells was measured on the density of their axons arriving to the neocortex. Cholinergic fibers were immunostained by antibody against choline-acetyltransferase (ChAT). Activated microglia was visualized by immunostaining against integrin αM [CD11b]. Image analyses of the immunostained anatomical structures were carried out on a Quantimet Q-5001W computerized imaging platform (Leica). Cholinergic fiber loss in the parietal neocortex layer V and the extent of microglial activation around the NBM and cortical lesion sites were then evaluated.

**Results:** Aβ1–42 did not influence open-field behaviour but significantly decreased attention performance in the novel object recognition test by 60% and attenuated passive avoidance learning by 67% (both significant at $p < 0.05$ level). Furthermore, it decreased cholinergic fiber density in the target neocortical area against sham-lesioned control ($p < 0.005$) and increased microglial activation around the lesion areas, i.e. the increment in NBM was 69% ($p < 0.01$) and in the neocortex 55% ($p < 0.05$). Memantine treatment significantly attenuated the behavioural deficits in attention and passive avoidance learning and the performance of memantine-treated Aβ1–42-lesioned group was not different from that of sham-lesioned control group. Memantine treatment prevented the Aβ1–42-induced cholinergic fiber loss in the neocortex ($p < 0.01$) and the degree of fiber loss in the lesioned animals was not different from control. In addition, memantine significantly attenuated microglial activation in the NBM (45%) and in the neocortical (35%) lesion sites.

**Conclusions:** It is concluded from these studies that (1) pre- and postlesion continuous treatment with memantine attenuates Aβ1–42-induced attention and learning deficits and (2) provides neuroprotection against Aβ1–42 toxicity on cholinergic neurons under the conditions studied. A putative rescuing action of memantine on other neuron systems damaged by Aβ1–42 as compared to cholinergic one merits further studies.

### References

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## P.5.b.006 Age-dependent changes in hippocampal glutamate levels parallel learning impairment in APP/PS1 transgenic mice

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**Background:** Several lines of evidence suggest that in Alzheimer's disease (AD), the neurotoxicity caused by β-amyloid (Aβ) peptides may be related to elevated levels of glutamate and/or overactivity of the NMDA receptors. We have earlier shown that memantine (an NMDA receptor antagonist) improves spatial learning in APP/PS1 transgenic mice with elevated levels of $A\beta_{40}$ and $A\beta_{42}$.

**Objective(s):** In the present study, we determined the extracellular levels of glutamate in the hippocampus of APP/PS1 mice at 6 and 16 months of age.

**Methods:** Extracellular levels of glutamate were measured by in vivo microdialysis under basal and stimulated conditions (in the absence or presence of KCl, respectively). A separate group of 6- and 16-month old APP/PS1 mice were also tested for spatial learning in the water maze, and their brain Aβ levels, amyloid plaque burden, microgliosis and astrogliosis were determined by ELISA and immunocytochemistry.

**Results:** APP/PS1 mice exhibited impaired performance in the water maze at 16 months but not at 6 months. Although some plaques were present at 6 months of age, the brain levels of $A\beta_{40}$, $A\beta_{42}$ and plaque pathology increased significantly from 6 months to 16 months. The basal extracellular glutamate level in the hippocampus did not change at either age in APP/PS1 mice, but the stimulated glutamate level was slightly higher at 6 months and significantly lower at 16 months compared to respective age-matched wild-type controls. Basal but not peak glutamate release correlated with the levels of vesicular glutamate transporters. The number of reactive microglia was elevated at 16 but not at 6 months.

**Conclusions:** The time course of amyloid pathology and cognitive dysfunction in this APP/PS1 mouse line suggest that the observed cognitive impairment in these mice was likely associated