Memantine Rescues Cholinergic Neurons from the Neurotoxic Effects of β-Amyloid (Aβ1-42)
Nyakas, C.; Szabó, R.; Penke, B.; Luiten, P.G.M.; Banerjee, P.K.

Published in:
European Neuropsychopharmacology

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
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.

Memantine rescues cholinergic neurons from the neurotoxic effects of β-amyloid (Aβ1–42)

C. Nyakas1, *, R. Szabó1, B. Penke2, P.G.M. Luiten3, P.K. Banerjee4, 1Ssemhevis University, Brain Physiology Research Group, Budapest, Hungary; 2Szeget University, Department of Medical Chemistry, Szeget, Hungary; 3University of Groningen, Department of Molecular Neuroscience, Groningen, Netherlands; 4Forest Research Institute, Department of Pharmacology and Toxicology, Jersey City, USA

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 1–4 days after 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 lesioning. At the end of chronic memantine treatment (10 days after lesioning) the animals were sacrificed for histological examination. The impact of amyloid peptide toxification 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 QuantiQimet 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