Program#/Poster#: 903.6/Z23

Title: Magnetic resonance imaging (MRI) reveals that galantamine effectively prevents morphological changes in the brain of guinea pigs challenged with lethal doses of soman

Location: San Diego Convention Center: Halls B-H

Presentation Start/End Time: Wednesday, Nov 07, 2007, 2:00 PM - 3:00 PM

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Organophosphorus compounds (OPs) are a class of highly toxic substances that includes a number of pesticides as well as the deadly nerve agents soman, sarin, tabun and VX. Multiple mechanisms of action, including the irreversible inhibition of acetylcholinesterase, account for their toxicity. We have previously demonstrated that treatment of male guinea pigs with galantamine effectively prevents the lethality and acute toxicity of the nerve agents soman, sarin, and VX. However, it is hitherto unknown whether this antidotal therapy counteracts the morphological changes that occur in the brain following an acute exposure to lethal doses of these nerve agents *in vivo*. In the present study, we used a clinical 3.0 Tesla MRI scanner to examine the time course of the morphological alterations that occurred in the brain of 6 male and 6 female prepubertal guinea pigs challenged with a single subcutaneous (sc) injection of soman. We also examined the brains of 6 guinea pigs (3 males and 3 females) that were treated with galantamine and challenged with soman. Each animal was imaged four times over seven days. In the first experimental group, guinea pigs were challenged with soman (28 µg/kg, sc) and treated 1 min later with atropine methyl nitrate (10 mg/kg, im). High resolution images (300-µm inplane resolution, 0.5-mm slice thickness) were obtained using an inversion recovery pulse sequence with an inversion time of 300 ms and a TE/TR of 15 ms/3000 ms. Changes in the piriform cortex, the hippocampus, the olfactory bulb and the amygdalar regions were visible seven hours after the soman challenge. These changes correlated strongly with the animals' behavior; the more severe the trembling, bruxism and convulsions, the more prominent the morphological aberrations. Segmentation of the brain into gray, white and CSF volumes revealed significant brain atrophy as observed by 27% increase in brain CSF at 30 hours ($p<0.05$). Concomitantly there was a significant accumulation of iron in the deep brain structures suggesting cell lysis particularly in the basal ganglia. No significant morphological changes were observed in the brains of galantamine-treated, soman-challenged guinea pigs; only minor damage was observed in the piriform cortex of some of these animals. The results presented herein suggest that the neurotoxic effect of the soman can be rapid and morphological changes in the brain following an acute exposure to soman is easily detected using MRI. Our findings also reveal that the galantamine-based antidotal therapy significantly limits the neuronal loss and the overall brain damage induced by soman.

Disclosures: **R. Gullapalli**, None; **Y. Aracava**, None; **E. Helal-Neto**, None; **G. Makris**, None; **J. Zhuo**, None; **E.F. Pereira** , None; **E.X. Albuquerque**, NIH Grant UO1NS059344-01, B. Research Grant (principal investigator, collaborator or consultant and pending grants as well as grants already received).

Support: NIH Grant U01NS059344

ARO Grant W911NF-06-1-0098

[Authors]. [Abstract Title]. Program No. XXX.XX. 2007 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2007. Online.

writing by SfN office prior to publication.