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Title: Galantamine prevents organophosphorus-induced cell death in the guinea pig telencephalon

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Authors: **I. MERCHENTHALER**[1], Y. ARACAVA[2], A. PUSKAR[1], E. F. R. PEREIRA[2], *E. X. ALBUQUERQUE[2];
[1]Depts. Epidemiol. and Anat. & Neurobiology, [2]Dept Pharmacol Exp Ther, Univ. Maryland Sch. Med., Baltimore, MD

Organophosphorus compounds (OPs) are a class of highly toxic substances that includes a number of insecticides and the deadly nerve agents soman, sarin, and VX. Numerous actions, including irreversible inhibition of acetylcholinesterase, contribute to the acute toxicity of these agents. A recent study demonstrated that galantamine, a drug used to treat Alzheimer's disease, is an effective medical countermeasure against OP toxicity (PNAS 103:13220, 2006). This study was designed to determine the effectiveness of galantamine in preventing cell death in the telencephalic brain areas that are mostly sensitive to the toxic effects of OPs, i.e. the hippocampus, the amygdala, and the cerebral cortex. Young, prepubertal male and female guinea pigs were given galantamine (8 mg/kg, im) or saline at 30 min before their subcutaneous challenge with 1.3-1.4xLD50 of soman, sarin or VX. All animals were treated with atropine immediately after the OP challenge. All galantamine-treated, OP-challenged guinea pigs survived with no signs of toxicity. In contrast, only 15% of the saline/atropine-treated, OP-challenged animals survived. The neuroprotective effect of galantamine was evaluated with FluroJade-B (FJ-B) staining and with *in situ* hybridization histochemistry to evaluate neurogranin gene expression. FJ-B labeling revealed dying cells, while the presence of neurogranin (a Ca^{2+}-binding protein in the telencephalon) transcripts indicated live neurons. Guinea pigs were transcardially perfused with buffered paraformaldehyde or formalin for FJ-B staining. For *in situ* hybridization, we used frozen, unperfused brains. Brain sections of 30-µm thickness were stained with FJ-B. Cryostat brain sections of 20-µm thickness were hybridized for neurogranin mRNA. Large numbers of FJ-B-positive neurons were observed in the hippocampus (primarily in CA1 region), piriform cortex and amygdala of saline/atropine-treated, OP-challenged animals. The reduced neurogranin mRNA expression in all three brain regions of saline/atropine-treated, OP-challenged animals was consistent with the loss of neurons in these brain areas. In the brains of galantamine/atropine-treated, OP-challenged animals, expression of neurogranin mRNA was comparable to that of naive animals. The absence of FJ-B positive neurons in the animals treated with galantamine/atropine and challenged with OPs suggests a neuroprotective action of galantamine. These studies provide morphological support for galantamine as an effective neuroprotector against OP toxicity.

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