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Title: Effects of galantamine on spontaneous inhibitory and excitatory postsynaptic currents in hippocampal CA1 pyramidal cells of guinea pigs challenged with soman

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We have demonstrated that a galantamine-based therapy effectively protects guinea pigs from the acute toxicity of lethal doses of organophosphorus compounds (OP) [PNAS 103:13220, 2006]. However, the mechanisms underlying galantamine's antidotal effectiveness are not fully understood. Here, we examined synaptic transmission in hippocampal slices from untreated and galantamine/atropine-treated guinea pigs challenged with soman. Spontaneous inhibitory and excitatory postsynaptic currents (sIPSCs and sEPSCs, respectively) were recorded from CA1 pyramidal neurons using the whole-cell patch-clamp technique. Hippocampal slices were obtained from 35-45-day-old female guinea pigs at 1 or 24 h after their treatments. Animals were divided into three groups according to the treatments they received. Group I received an intramuscular (i.m.) saline (0.5 ml/kg). Group II received a subcutaneous (s.c.) injection of 1xLD50 soman (26 µg/kg). Group III received galantamine (8 mg/kg, i.m.) at 30 min before and atropine (10 mg/kg, i.m.) at 1 min after 1.6xLD50 soman (42 µg/kg, i.m.). In slices obtained at 1 or 24 h after the challenge of the guinea pigs with soman, the sIPSC and sEPSC frequencies were significantly lower than those observed in slices from control animals (Table 1). In slices obtained from galantamine/atropine-treated guinea pigs at 1 or 24 h after their challenge with soman, the frequency of sIPSCs was significantly higher than those observed in slices from control animals (Table 1). Further, in slices from galantamine/atropine-treated, soman-challenged animals, the frequency of sEPSCs recorded from CA1 pyramidal neurons was comparable to that observed in slices from control animals (Table 1). The amplitude distributions of sIPSCs and sEPSCs were not significantly different among the experimental groups. An increased inhibitory tone in the hippocampus of animals treated with galantamine would contribute to its antidotal effectiveness against OP toxicity.

Table 1

	sIPSC frequency (Hz)		sEPSC frequency (Hz)	
	1 h	24 h	1 h	24 h
Control (Group I)	0.89 ± 0.27	0.93 ± 0.17	0.70 ± 0.06	0.76 ± 0.06
Soman (Group II)	0.25 ± 0.08 *	0.52 ± 0.07 *	0.44 ± 0.14 *	0.30 ± 0.13 *
Galantamine/Soman/ Atropine (Group III)	1.52 ± 0.30 *†	1.28 ± 0.24 *†	0.91 ± 0.68 †	0.67 ± 0.06 †

Student's t-test: * $p < 0.05$ (groups II and III vs. group I); † $p < 0.05$ (group III vs. group II); n = 3-10 neurons/group.

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