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EFFECT OF PHYSOSTIGMINE PRETREATMENT ON PARATHION TOXICITY IN RATS

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Abstract The protective effects of physostigmine against the toxicity of parathion (diethyl-4-nitrophenyl phosphorothionate) were examined in male Sprague-Dawley rats. Physostigmine (100 or 1,000 mg/kg, ip) injected 30 min before decreased the inhibition of acetylcholinesterase (AChE) activities in brain, lung and blood induced by parathion (2 mg/kg, ip). Physostigmine pretreatment did not affect the total hepatic microsomal cytochrome P450 (CYP) or cytochrome b5 contents. There was no change in p-nitrophenol hydroxylase, p-nitroanisole demethylase or aminopyrine N-demethylase activities in liver of physostigmine-pretreated rats. However, erythromycin N-demethylase activity, a selective CYP3A marker, was significantly inhibited by the carbamate in a dose-dependent manner. Physostigmine also decreased erythromycin N-demethylase activity in brain. Physostigmine did not alter carboxylesterase or paraoxonase activity, indicating that detoxication of parathion was not affected by this carbamate. The pharmacokinetic parameters of parathion (3 mg/kg, iv) were determined after a single dose of physostigmine. In physostigmine-pretreated rats, the area under the curve (AUC) of parathion was significantly greater; clearance (Cl) was lower than control rats. Physostigmine (100 or 1,000 mg/kg/day, ip) was repeatedly administered to rats for 7 consecutive days. When parathion was given to rats 4 or 24 hr after the final dose of the carbamate, the brain AChE inhibition was reduced significantly. Repeated administration of physostigmine did not affect erythromycin N-demethylase activity or the pharmacokinetic parameters of parathion. However, there was a significant decrease in specific [^{3} H] QNB binding in striatum and hippocampus. Scatchard analysis revealed a significant decrease in Bmax without a change in Kd. The result suggest that the inhibition of CYP3A play an important role in the decrease of parathion toxicity provided by an acute dose of physostigmine, but changes in characteristics of muscarinic receptor could account for the protection against parathion toxicity in rats treated with this carbamate repeatedly.

keyword : physostigmine, parathion, acetylcholinesterase inhibition, muscarinic receptor