

75. SCAVENGER PROTECTION AGAINST ORGANOPHOSPHORUS AGENTS BY CHOLINESTERASES

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The difficulty in providing protection against rapidly aging organophosphorus (OP) agents with current drug regimens led to the development of scavenger protection against OP agents in which a protein scavenger circulating in the blood stream inactivates the OP agent before it can produce its toxic effect. The most extensively tested and developed of these OP scavengers are the cholinesterases whose effectiveness in protecting against OP agents has been demonstrated in a variety of rodent and nonhuman primate models. In comparison to atropine/oxime treatment or pyridostigmine pretreatment, fetal bovine serum (FBS) AChE pretreatment provided better protection against postexposure incapacitation in mice challenged with 8 x LD₅₀ of soman. Similarly, rhesus monkeys pretreated with FBS AChE, equine serum BChE or human serum BChE were protected against 3.0–5.0 x LD₅₀ of soman and were free of behavioral incapacitation as measured by either serial probe recognition or by a primate equilibrium platform or by spatial discrimination tasks. The effectiveness of scavenger protection in preventing postexposure incapacitation has also stimulated efforts to amplify the effectiveness of enzyme scavenger protection by oxime reactivation of OP-inhibited scavenger. The combination of HI-6 with AChE pretreatment increased the amount of sarin that could be detoxified. In addition, combining OP hydrolase with oxime/cholinesterase detoxification extends its efficacy to all nerve agents and pesticides. The success of recent efforts to increase OP/scavenger stoichiometry by developing AChE mutants that are more resistant to aging or more easily reactivated than wild-type AChE suggests that future OP scavengers will produce even greater levels of medical protection.

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