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Development of orally bioavailable, blood-brain barrier penetrant antidotes to replace 2-PAM as an antidote in organophosphate exposure

Current antidotes to organophosphate exposure from pesticides and the more insidious nerve agents of terrorism are limited by their inability to cross the blood-brain barrier, their rapid clearance and lack of oral bioavailability. To enhance antidote activity, we have developed a library of zwitterion antidotes with measured *in vitro* reactivation capabilities and capacity to cross the blood-brain barrier and reactivate cholinesterase in the central and peripheral nervous system. Lead compounds show good protection ratios in mice and have led to more detailed pharmacokinetic and tissue disposition studies in mice and macaques. Antidotes, in contrast to therapeutic agents in treatment of chronic disease, require immediate absorption and distribution to the target tissue of action. To this end, we have developed a small molecule intramuscular loading dose-oral maintenance dose scheme for the treatment of organophosphate poisoning from nerve agents used in terrorism and pesticides used in agriculture and home/gardens. By virtue of the ionization equilibria transitioning at physiological pH values between amine cation and oximate anion, both with pKa values between 8 and 9, a cationic or zwitterion species is available for reactivation of organophosphate conjugated AChE within the active center gorge in target tissues and a neutral species, that can readily cross the blood-brain barrier and exhibit oral bioavailability, treatment immediately after exposure by subcutaneous organophosphates or inhaled sarin vapor reverses toxicity in mice and macaques. The presentation will review the pharmacokinetics and tissue disposition required for successful antidote treatment of terrorism-inspired events.

Biography

Palmer Taylor is a PhD holder and the Sandra and Monroe Trout Chair Person of Pharmacology at the University of California, San Diego. He served as Founding Dean of the Skaggs School of Pharmacy and Pharmaceutical Sciences (2002-2014) and previously as Chair Person of the Department of Pharmacology in the School of Medicine (1987-2002). His research is directed to molecular pharmacology and neurotransmission, through study of the structures and functions of acetylcholinesterase (AChE) and nicotinic acetylcholine receptors (nAChRs). His particular interests are molecular recognition and design of selective therapeutic agents, directed to the α7-nAChR subtype and to antidotes that reactivate the organophosphate-conjugated AChE. The soluble acetylcholine binding protein has been the template for design of agonists and antagonists of the α7-nAChR subtype potentially useful in treatment of disorders of nervous system development and aging. His group has also been responsible for development of small zwitterion antidotes that serve as reactivators for organophosphate poisoning.

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