Mechanism of Organophosphate Development Neurotoxicity

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There is increasing concern that perinatal exposure to organophosphate acetylcholinesterase (AChE) inhibitors (OPs) may cause cognitive problems in children. This concern is based on recent reports of widespread exposure of the public to OPs, and on animal studies indicating that the developing nervous system is more sensitive than the mature nervous system to the neurotoxic effects of OPs. It is reported that OPs cause developmental neurotoxicity at doses significantly below those that inhibit the catalytic activity of AChE. These data have been widely interpreted to mean that OPs target molecules other than AChE. However, recent evidence demonstrating that AChE functions to promote axonal growth in the developing but not mature neurons suggest an alternative explanation: OPs target AChE, but the mechanism of developmental neurotoxicity involves disruption of the morphogenic function of AChE not inhibition of its catalytic activity. Interference with the axon- promoting activity of AChE represents a biologically plausible mechanism for explaining the functional deficits observed in animals exposed perinatally to OPs. The goal of this proposal is to test the hypothesis that OPs disrupt axonal growth by interfering with the morphogenic activity of AChE. The specific aims are to: (1) Validate sympathetic and dorsal root ganglion (DRG) neurons as a model system for mechanistic studies of OP-induced axonal dysmorphogenesis; and (2) Determine if AChE mediates OP effects on axonal growth. Neurons cultured from AChE wildtype (+/+) and AChE null (-/-) mice will be exposed to varying levels of chlorpyrifos (CPF) or its metabolites CPF-oxon (CPFO) and 3,5,6-trichloro-2-pyridnol (TCP). The number, length, and branching patterns of axons and dendrites will be quantified using Metamorph imaging software following immunocytochemical localization of axon- or dendrite-specific antigens. AChE enzymatic activity will be measured using a standard colorimetric assay; and cell viability, by assessing protein synthesis. These data will not only provide mechanistic insight into the developmental neurotoxicity of OPs, but also suggest a biological basis for the increased vulnerability of the developing nervous system. Impacts of these studies include the reduction of uncertainty in risk assessment, the development and evaluation of biomarkers for OP toxicity in children, and the design of in vitro assays for screening the developmental neurotoxicity of other OPs of concern.

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Presentation(s):

Howard A.S., Bucelli R., Jett, D.A., Lein, P.A. (2003). Chlorpyrifos inhibits axon outgrowth in primary cultures of peripheral neurons through inhibition of the morphogenic activity of acetylcholinesterase. Presentation at the Society of Toxicology Annual Meeting.

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Jett, D.A., Lein, P.J. (In press) Non-cholinesterase mechanisms of central and peripheral neurotoxicity: Muscarinic receptors and other targets. In: Toxicology of Organophosphates and Carbamate Pesticides (Gupta RC, ed) Elsevier, San Diego, CA.

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