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NEUROTOXIC EFFECTS OF ORGANOPHOSPHORUS COMPOUNDS.

Djumaniyazov Shavkat Atanazarovich

Samarkand State Medical University, Department of Physiology. Samarkand, Uzbekistan

Conclusion. *Irreversible inhibition of acetylcholinesterase (AChE) in the nervous system causes cholinergic syndrome during acute exposure to organophosphorus compounds (Goncharov N.V.; 2023). However, according to the researchers, it is assumed that other mechanisms of action specific to these compounds contribute not only to the acute toxicity of high doses of these insecticides, but also to the neurotoxic effects that develop after prolonged exposure to low doses, especially in the developing brain (Djumaniyazov Sh.A. 2022-2024).*

Based on the concept that AChE is the primary molecular target responsible for the acute toxicity of organophosphorus (OP) species, the LD_{50} of these insecticides should directly correlate with their IC_{50} for enzyme inhibition and/or the rate of reactivation of the inhibited enzyme.

AChE inhibition is a common mechanism underlying OP neurotoxicity to the nervous system, and it can be predicted that exposure of a developing organism to any OP will cause exactly the same effect with a biological gradient proportional to the degree of inhibition of AChE activity. Exposure of developing organisms to different OPs causes different effects. Numerous studies have demonstrated that chlorpyrifos (CPF) can directly interact with and alter the activity of serine hydrolases, including carboxylesterases, muscarinic receptors, cannabinoid receptors, and structural proteins such as tubulin (Basharina A. A.; 2022).

Keywords: *acetylcholinesterase, neurotoxicity, chlorpyrifos, organophosphorus compounds.*

Introduction. Some studies have suggested that the disruption of the structural and functional integrity of the brain following low-level CPF exposure may result from impaired axonal transport and growth mediated by tubulin and its associated structural proteins (Djumaniyazov Sh.A.). Subsequent studies have shown that organophosphorylated tubulin and disrupted microtubule structures can be detected in the brains of adult female mice treated with doses of CPF that did not cause significant inhibition of AChE (3 mg/kg/day, 14 days, s.c.) (Jiang et al . 2010). It can be speculated that impaired axonal transport and growth resulting from direct interactions of CPF and/or CPF-oxon with structural proteins in the developing brain may generate abnormal patterns of neuronal connectivity and thus contribute to the neurobehavioral changes reported to be associated with CPF exposure during development.

The work of Yang et al. (2008) demonstrated that at doses that do not inhibit the catalytic activity of AChE, CPP (1 nM) and CPP-oxon (1 pM) inhibit neurite outgrowth in rats and mice. These results indicate that the ability of CPP and CPP-oxon to inhibit neurite outgrowth: 1. depends on their ability to block the catalytic activity of AChE, and 2. cannot be explained solely by a direct interaction of CPP and/or CPP-oxon with structural proteins. They also suggest that the inhibition of AChE morphogenetic activity caused by CPP/CPP-oxon may contribute to the neurotoxicity of insecticide concentrations that are insufficient to inhibit the catalytic activity of the enzyme.

Additional mechanisms contributing to the developmental neurotoxicity of CPF include: exacerbation of oxidative stress (Slotkin 2021), imbalance in intracellular Ca 2+ homeostasis, increased signaling mediated by inflammatory mediators such as interleukins and cytokines (Tian et

al . 2021), and increased activity/expression of protein kinases including protein kinase C and mitogen-activated kinases (Zhang et al . 2021).

In recent years, attention has been directed to epigenetic mechanisms that play a critical role in the development of the nervous system as potential determinants of the etiology of neurological disorders resulting from exposure of the developing brain to toxic substances such as heavy metals and insecticides.

Exposure of pregnant mice to CPF-methyl, chemically similar to CPF but less acutely toxic than CPF, was shown to cause dose-dependent hypomethylation of the H19 gene in various organs of the fetuses at GD13.

Conclusions

Various studies worldwide have shown that CPF is a developmental neurotoxicant. The neurotoxicity of CPF has been documented in studies using a variety of animal models, routes of exposure, and testing methods, and is generally characterized by cognitive deficits and disruption of the structural integrity of the brain. However, there is still debate about whether the effects observed in animal models can be extrapolated to humans exposed to low levels of CPF.

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