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Peaceful use of disastrous neurotoxicants

Yoram Finkelstein [a,*], Dejan Milatovic [b], Philip Lazarovici [c], Amit Ophir [a], Elihu D. Richter [d], Michael Aschner [b], Shimon Lecht [c], Cezary Marcinkiewicz [f], Peter I. Lelkes [g], Snjezana Zaja-Milatovic [b], Ramesh C. Gupta [b], Berta Brodsky [e], Avigail Rosengarten [e], Elena Proscura [e], Elena Shapira [e], Uri Wormser [e]

[a] Service and Unit of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel
[b] Vanderbilt University School of Medicine, Department of Pediatrics/Pediatric Toxicology, Nashville, TN, USA
[c] The Laboratory of Neuropharmacology, Neuro-oncology and Neural Engineering, Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University, Jerusalem, Israel
[d] Occupational and Environmental Medicine Hebrew University-Hadassah School of Public Health and Community Medicine, Jerusalem, Israel
[e] Institute of Drug Research, School of Pharmacy, Faculty of Medicine, Institute of Life Sciences, The Hebrew University, 91120 Jerusalem, Israel
[f] Department of Biology, Temple University, Philadelphia, PA 19122, USA
[g] Laboratory of Cellular Tissue Engineering, School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA 19104, USA

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ABSTRACT

The increasing exposure to environmental neurotoxicants in the last decades caused serious health problems in the world population. Some of the neurotoxic agents are being used in agriculture and household such as insecticides and rodenticides and others are of natural origin like snake and scorpion venoms. Additional group of harmful substances is the chemical warfare agents including nerve and blistering agents that are known for their disastrous effects on neuronal tissues. The present paper presents a combination of epidemiological/clinical and molecular approaches for investigating the effect of certain groups of neurotoxicants on a variety of pathologies.

The work of Finkelstein and coworkers describes epidemiological and clinical studies on acute and chronic organophosphate (OP)-induced neurotoxicity in certain populations in Israel. They mainly investigated the neurotoxic effects of low-level long-term exposure to OP in agricultural areas but also dealt with acute exposures as well. A molecular approach to OP mechanism of neuronal injury was described by Milatovic and coworkers. They demonstrated OP-induced oxidative injury in pyramidal neurons in the CA1 hippocampal area and its suppression by antioxidants. Lecht and coworkers described the novel snake venom angioneurins as important mediators of the physiological cross-talk between the cardiovascular and nervous systems. They also showed that under certain conditions these angioneurins may induce pathologies such as tumor development or disruption of the vascular barrier function during envenomation. Additional mechanistic/therapeutic approach was presented by Brodsky, Rosengarten, Proscura, Shapira and Wormser. They developed a novel anti-inflammatory peptide that reduced skin irritation induced by heat and sulfur mustard (SM) stimuli. Since SM causes neuropsychiatric symptoms and alterations in neurological functions this peptide may serve as a potential treatment of neuronal injuries caused by environmental neurotoxicants.

These reviews highlight different aspects of neurotoxicity, addressing epidemiology and mechanisms of toxicity; and identifying novel potential therapies.

IsIs there a consistent cognitive and neurobehavioral pattern of toxicity following acute, delayed or chronic exposures to organophosphates?

Yoram Finkelstein[1*], Amit Ophir[1], Michael Aschner[3], Elihu D. Richter[2]

[1]Service and Unit of Neurology and Toxicology, Shaare Zedek Medical Center, Jerusalem, Israel

* Corresponding author at: Service and Unit of Neurology and Toxicology, Shaare Zedek Medical Center, P.O. Box 3235, Jerusalem 91031, Israel. Tel.: +972 2 6555655; fax: +972 2 6781781.
E-mail addresses: yoramf@ekmd.huji.ac.il, yfinkelstein@bezeqint.net (Y. Finkelstein).

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[2]The Department of Occupational and Environmental Medicine Hebrew University-Hadassah School of Public Health and Community Medicine, Jerusalem, Israel

[3]Department of Pediatrics, Department of Pharmacology, and the Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, TN 37232, USA

* Corresponding author. Tel.: +972 2 6555655; fax: +972 2 6666941.

Email address: yoramf@ekmd.huji.ac.il (Y. Finkelstein)

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Introduction

Interest in the neurotoxic effects of organophosphates (OPs) in humans began in 1932 when Longe and von Krueger noted the self-toxic effects of the vapors of OP compounds which they just had synthesized (Besser and Guttman, 1995). Since then, intense research has being carried out. Most of the studies have dealt with acute OP neurotoxicity, probably because the potential use of OP warfare remains a serious concern. Thus, worldwide interest in OP has been aimed at the acute clinical manifestations following short-term high-dose exposure.

Most of the research on agricultural OP poisoning, an additional worldwide problem (World Resources Institute, 1994–1995) has also been dedicated to the acute clinical picture and to the life-saving procedures. The more subtle central nervous system (CNS) effects, first and foremost the impairment in higher cognitive functions, have received less attention (Steenland et al., 1994; Steenland, 1996).

The first study dedicated to the possible linkage between acute OP poisoning and chronic neurobehavioral changes was carried out in 1950. In this clinical study, two patient groups (affective bipolar and schizophrenic patients) and a healthy control group were injected daily with diisopropylfluorophosphate (DFP) for one week. Depressive mood was observed in the bipolar patients and in the normal controls, while behavioral deterioration and lengthy exacerbation of psychosis were observed in the schizophrenic patients (Rowntree et al., 1950). Similar schizophrenic and depressive symptomatology was described a decade later in patients who had been chronically exposed to OP for several years (Gershon and Shaw, 1961), but a detailed epidemiological study (Stoller et al., 1965) challenged these earlier observations. Later studies which employed neurobehavioral test batteries, showed a sub-clinical decrease in the cognitive performance of individuals who had previously had a single (Rosenstock et al., 1991) or repeated episodes (Savage et al., 1988) of acute OP poisoning.

The delayed CNS effects of acute OP poisoning have also been described scantily.

Neurophysiologic outcomes were detectable months or even years following recovery from acute OP poisoning (Savage et al., 1988; Yokoyama et al., 1998).

Recently, a dose–response association was found between low-dose inhalation exposure to the OP warfare agents sarin and cyclosarin during the 1991 Gulf War and delayed impaired neurobehavioral functioning as well as subtle CNS pathology as revealed by a magnetic resonance imaging (MRI) study (Heaton et al., 2007; Proctor et al., 2006).

The effects of low-level long-term exposures have attracted more attention, due to the increasing concern on the health hazards of the widespread use of pesticides in agricultural communities. However, studies designed to examine the possible neurobehavioral effects of chronic exposures are relatively sparse. In most of the studies, there are considerable uncertainties regarding exposures. Evidently, human exposures include other classes of pesticides such as fungicides and fumigants. Furthermore, most of the exposures are to mixtures of chemicals. Neurobehavioral test batteries showed several effects of chronic OP exposure in adult working populations: deficits in measures of motor speed and coordination, sustained attention, and information processing speed (Reidy et al., 1992; Steenland et al., 1994). Neurobehavioral changes have also been reported in farm workers in Florida (Kamel et al., 2003): farm work was associated with poor performance on Digit Span, tapping, and Santa Ana Tests. In cotton pesticides applicators in Egypt presumed to have heavy exposures, a broad range of signs was observed: visual motor slowliness, reduced verbal abstraction, attention deficit and memory impairment (Farahat et al., 2003).

Association of long-term exposure and worse performance in neuropsychological functions was shown in a cross-sectional survey of greenhouse workers in high-exposure conditions in Spain. The study was performed, using a wide array of tasks to test neuropsychological functioning and emotional status. The variable "years working with pesticides" was found to be a measure of cumulative exposure for risk of worsened perceptive function performance, visuomotor praxis and integrative task performance time with no relation to plasma ChE activity as a measure of recent exposure (Roldán-Tapia et al., 2005).

However, the studies of subjects with long-term low-level OP exposures show overall inconsistent findings, and only few studies have reported the association between pesticide exposure and neurological endpoints (Rothlein et al., 2006). Evidently, OP may produce a spectrum of clinical manifestations in human, ranging from convulsion and cardiac arrhythmia, coma and death (at the high-end acute exposures) to sub-clinical neurotoxicity with implicit cognitive deficits and mild neurobehavioral impairments (at the low-end chronic exposures). But the clinical and sub-clinical signs have not painted a comprehensive and consistent clinical picture, and no well-defined anatomical common denominator has yet been defined. Furthermore, there is no clear distinction among the different clinical forms of OP poisoning following different rates and duration of exposures and the clinical data are sometimes conflicting.

Several studies in Israel on acetyl cholinesterase (AChE) inhibitors (excluding carbamates) have tried to resolve this conflicting evidence and to find a common denominator for the gamut of clinical manifestations. Several approaches have been undertaken to address this question: (a) quantitative histochemical analysis of AChE activity in fatal cases of acute OP poisoning; (b) a clinical study on severe acute consecutive cases of OP poisoning; (c) studies on the neurobehavioral effects of low-level short-term OP exposure in Israel; (d) an observational clinical study on the delayed sequelae of acute OP poisoning; (e) epidemiological field studies on the effects of low-level long-term OP exposure in the 1980s; (f) current re-examination of the same cohorts by the same as well as novel methods.

The principal clinical findings of all the studies on the neurobehavioral effects of OP poisonings which have been carried out in Israel between 1970 and 2010 are summarized herein and may well provide the Israeli perspective.

(a) Quantitative histochemical analysis of acetyl cholinesterase (AChE) activity in the human brain in severe acute cases of OP poisoning

For nearly four decades, OP pesticides have been the most commonly used pest-control agents in cotton and orchard cultivation in Israel (Richter et al., 1992a,b; Bar-Ilan et al., 2000; Bar-Ilan and Malman, 2007). Most reported instances of acute OP poisoning in Israel have been due to agricultural pesticides (Finkelstein et al., 1988a,b; Weissmann-Brenner et al., 2002). Quantitative histochemical analysis of brain AChE activity was