Nerve agent intoxication: recent neuropathophysiological findings and subsequent impact on medical management prospects. [Review]

Collombet JM.
[Journal Article. Research Support, Non-U.S. Gov't. Review]

UI: 21791221

This manuscript provides a survey of research findings catered to the development of effective countermeasures against nerve agent poisoning over the past decade. New neuropathophysiological distinctive features as regards organophosphate (OP) intoxication are presented. Such leading neuropathophysiological features include recent data on nerve agent-induced neuropathology, related peripheral or central nervous system inflammation and subsequent angiogenesis process. Hence, leading countermeasures against OP exposure are down-listed in terms of pre-treatment, protection or decontamination and emergency treatments.

The final chapter focuses on the description of the self-repair attempt encountered in lesioned rodent brains, up to 3 months after soman poisoning. Indeed, an increased proliferation of neuronal progenitors was recently observed in injured brains of mice subjected to soman exposure. Subsequently, the latter experienced a neuronal regeneration in damaged brain regions such as the hippocampus and amygdala. The positive effect of a cytokine treatment on the neuronal regeneration and subsequent cognitive behavioral recovery are also discussed in this review. For the first time, brain cell therapy and neuronal regeneration are considered as a valuable contribution towards delayed treatment against OP intoxication. To date, efficient delayed treatment was lacking in the therapeutic resources administered to patients contaminated by nerve agents. Copyright 2011 Elsevier Inc. All rights reserved.

Status
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Institution
Departement de Toxicologie, IRBA/CRSSA, 24 avenue des Maquis du Gresivaudan, B.P. 87, 38702 LA TRONCHE cedex, France. jmcollombet@imassa.fr

<td colspan=""/>
2. Biological markers of exposure to organophosphorus nerve agents. [Review]
Black RM. Read RW.
Archives of Toxicology. 87(3):421-37, 2013 Mar.
[Journal Article. Review]
UI: 23371414
Organophosphorus nerve agents are the most toxic chemical warfare agents that are known to have been produced, stockpiled and weaponised. Their development, production, stockpiling and use are prohibited under the terms of the Chemical Weapons Convention and, together with their precursors, are subject to strict controls and verification procedures. The detection and identification of biological markers of exposure to nerve agents are required for three main purposes: confirmation of exposure for forensic purposes in cases of alleged use; diagnosis to guide appropriate medical countermeasures in the event of an exposure; and occupational health monitoring of workers in defence laboratories and demilitarisation facilities. Biomarkers of nerve agents fall into two main groups, free metabolites and adducts to proteins. These are reviewed together with analytical methods for their identification. Examples are provided of applications in cases of human exposure.

Status
MEDLINE

Institution
Defence Science and Technology Laboratory (Dstl), Porton Down, Salisbury, UK.
rmblack@dstl.gov.uk

3. Clinical and paraclinical guidelines for management of sulfur mustard induced bronchiolitis obliterans; from bench to bedside. [Review]
Saber H. Saburi A. Ghanei M.
Inhalation Toxicology. 24(13):900-6, 2012 Nov.
[Journal Article. Review]
UI: 23121299
It is well documented that inhalation of sulfur mustard (SM) causes injury to the respiratory system. Many Iranian civilians and war veterans are suffering from late respiratory complications of SM exposure. Recent studies have shown that bronchiolitis obliterans (BO) is the major cause of respiratory complications following SM exposure. In this review, we focus on the clinical, pulmonary, radiological, immunological and pathological manifestations in SM-induced BO with intent to provide a practical, clinical and paraclinical guideline for diagnosis and step-wise workup of these patients, which may be used to manage similar lung injuries induced by other similar inhaled toxins.

Status
MEDLINE
Institution
Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, I.R. Iran.

4. Delayed neurological complications of sulphur mustard and tabun poisoning in 43 Iranian veterans.
Darchini-Maragheh E. Nemati-Karimooy H. Hasanabadi H. Balali-Mood M.
[Journal Article. Research Support, Non-U.S. Gov't]
UI: 22762514

Delayed neurotoxic complications of chemical warfare agents (CWA), such as sulphur mustard (SM) and tabun, in human beings have not been reported in detail. We thus aimed to investigate possible neurotoxic complications of these agents in Iranian veterans 22-27 years after exposure. After co-ordination with the veteran foundation and obtaining the approval of the medical research ethics committee, 43 Iranian veterans with late complications of CWA exposure during the Iran-Iraq conflict were studied after obtaining signed written informed consent. Demographic and clinical findings were recorded on pre-designed forms. Neurological examination was performed by a neurologist. Routine biochemical tests were performed for all the patients. Electromyography (EMG), nerve conduction velocity (NCV) and electroencephalography (EEG) were carried out as clinically indicated. The majority of the patients (38) had been exposed to SM and only five patients to tabun. Hyperaesthesia was the most objective finding (72.1%). Fatigue (93%),
paraesthesia (88.3%) and headache (83.7%) were the most common subjective findings in the patients. Sensory nerve impairments, including paraesthesia (88.3%), hyperaesthesia (72.1%) and hypoesthesia (11.6%), were the most common observed clinical complications. EMG and NCV were impaired in seven patients (16.3%) who were all SM-exposed patients but did not show any significant correlation with organ complications. EEG was negative even in the seized patients. Cholesterol, LDL and triglyceride levels were significantly above the normal ranges. Late neurological complications of CWA, particularly SM poisoning, are considerable even after three decades of exposure and require medical attention. 2012 The Authors Basic & Clinical Pharmacology & Toxicology 2012 Nordic Pharmacological Society.

Status
MEDLINE
Institution
Medical Toxicology Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

5. Microbiological evaluation of chronic blepharitis among Iranian veterans exposed to mustard gas: a case-controlled study.
Karimian F. Zarei-Ghanavati S. A BR. Jadidi K. Lotfi-Kian A.
[Comparative Study. Journal Article]
UI: 21282998
PURPOSE: To evaluate the microbiological characteristics of eyelid margin flora in chronic blepharitis in mustard gas-exposed individuals and compare the results with those in age- and sex-matched unexposed people.
METHODS: In this comparative case series, 289 patients with ocular manifestations of mustard gas exposure (case) were evaluated for signs of chronic blepharitis. Additionally, microbiological evaluation of eyelid margins was conducted in these patients and compared with results of 100 unexposed patients with chronic blepharitis (control).
RESULTS: One-hundred fifty (52.0%) of 289 mustard gas casualties had signs of chronic blepharitis. Microbiological evaluation revealed higher isolation rates of Staphylococcus epidermidis (78%) and Staphylococcus aureus (57%) in the case in comparison to control group
Moreover, S. aureus isolated from the cases exhibited greater resistance to common antibiotics compared with control group. Fungi were isolated more frequent in the case compared with controls (30% vs. 4%, P < 0.01), with Cladosporium and Candida species being most common in the case group.

CONCLUSIONS: Exposure to mustard gas seems to alter the microbiological flora of the eyelid margin. Staphylococcus spp., including antibiotic-resistant strains, and fungi were more frequently isolated in these patients. The relationship between microbial culture results and the severity of ocular surface manifestations in mustard gas-injured cases warrant further investigation.

Status MEDLINE
Institution Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences, Labbafinejad Medical Center, Department of Ophthalmology, Tehran, Iran. karimianf@yahoo.com

6. Loss of expression of TGF-betas and their receptors in chronic skin lesions induced by sulfur mustard as compared with chronic contact dermatitis patients.
Khaheshi I. Keshavarz S. Imani Fooladi AA. Ebrahimi M. Yazdani S. Panahi Y. Shohrati M. Nourani MR.
BMC Dermatology. 11:2, 2011.
[Comparative Study. Journal Article. Research Support, Non-U.S. Gov't]
UI: 21235789
BACKGROUND: Sulfur mustard (SM) is a blister-forming agent that has been used as a chemical weapon. Sulfur mustard can cause damage in various organs, especially the skin, respiratory system, and eyes. Generally, the multiple complications of mustard gas result from its alkalizing potency; it reacts with cellular components like DNA, RNA, proteins, and lipid membranes. TGF-beta is a multi-functional cytokine with multiple biological effects ranging from cell differentiation and growth inhibition to extracellular matrix stimulation, immunosuppression, and immunomodulation. TGF-beta has 3 isoforms (TGF-beta 1, 2, 3) and its signaling is mediated by its receptors: R1, R2 and intracellular Smads molecules. TGF-beta has been shown to have anti-inflammatory effects. TGF-betas and their receptors also have an important role in modulation of
skin inflammation, proliferation of epidermal cells, and wound healing, and they have been implicated in different types of skin inflammatory disorders.

METHODS: Seventeen exposed SM individuals (48.47 ± 9.3 years), 17 chronic dermatitis patients (46.52 ± 14.6 years), and 5 normal controls (44.00 ± 14.6 years) were enrolled in this study. Evaluation of TGF-betas and their receptors expressions was performed by semiquantitative RT-PCR. Only TGF1 was analyzed immunohistochemically.

RESULTS: Our results showed significant decreases in the expression percentages of TGF-beta 1, 2 and R1, R2 in chemical victims in comparison with chronic dermatitis and normal subjects and significant decreases in the intensity of R1 and R2 expressions in chemical victims in comparison with chronic dermatitis and normal controls. (P value < 0.05)

CONCLUSIONS: TGF-betas and their receptors appear to have a noticeable role in chronic inflammatory skin lesions caused by sulfur mustard.

Status
MEDLINE
Institution
Chemical Injury Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.

7.
A high-throughput diagnostic method for measuring human exposure to organophosphorus nerve agents.

Knaack JS. Zhou Y. Abney CW. Jacob JT. Prezioso SM. Hardy K. Lemire SW. Thomas J. Johnson RC.


[Journal Article]

UI: 23083472

An automated high-throughput immunomagnetic separation (IMS) method for diagnosing exposure to the organophosphorus nerve agents (OPNAs) sarin (GB), cyclohexylsarin (GF), VX, and Russian VX (RVX) was developed to increase sample processing capacity for emergency response applications. Diagnosis of exposure to OPNAs was based on the formation of OPNA adducts to butyrylcholinesterase (BuChE). Data reported with this method represent a ratio of the agent-specific BuChE adduct concentration, relative to the total BuChE peptide concentration that provides a nonactivity measurement expressed as percent adducted. All magnetic bead transfer steps and washes were performed using instrumentation in a 96-well format allowing for simultaneous extraction of 86 clinical samples plus reference materials. Automating extractions increased sample throughput 50-fold, as compared to a previously reported manual method. The
limits of detection, determined using synthetic peptides, were 1 ng/mL for unadducted BuChE and GB-, GF-, VX-, and RVX-adducted BuChE. The automated method was characterized using unexposed serum and serum pools exposed to GB, GF, VX, or RVX. Variation for the measurement of percent adducted was <12% for all characterized quality control serum pools. Twenty-six (26) serum samples from individuals asymptomatic for cholinesterase inhibitor exposure were analyzed using this method, and no background levels of OPNA exposure were observed. Unexposed BuChE serum concentrations measured using this method ranged from 2.8 mug/mL to 10.6 mug/mL, with an average concentration of 6.4 mug/mL.

Status
MEDLINE
Institution
Emergency Response and Air Toxicants Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Highway, MS F44, Chamblee, Georgia 30341, United States.

8.
Highly sensitive and selective immuno-capture/electrochemical assay of acetylcholinesterase activity in red blood cells: a biomarker of exposure to organophosphorus pesticides and nerve agents.
Chen A.  Du D.  Lin Y.
[Journal Article.  Research Support, N.I.H., Extramural.  Research Support, Non-U.S. Gov't]
UI: 22208309
Acetylcholinesterase (AChE) enzyme activity in red blood cells (RBCs) is a useful biomarker for biomonitoring of exposures to organophosphorus (OP) pesticides and chemical nerve agents. In this paper, we reported a new method for AChE activity assay based on selective immuno-capture of AChE from biological samples followed by enzyme activity assay of captured AChE using a disposable electrochemical sensor. The electrochemical sensor is based on multiwalled carbon nanotubes-gold (MWCNTs-Au) nanocomposites modified screen printed carbon electrode (SPCE), which is used for the immobilization of AChE specific antibody. Upon the completion of immunoreaction, the target AChE (including active and inhibited) is captured onto the electrode surface and followed by an electrochemical detection of enzymatic activity in the presence of acetylthiocholine. A linear response is obtained over standard AChE concentration range from 0.1 to 10 nM. To demonstrate the capability of this new biomonitoring method, AChE solutions dosed
with different concentrations of paraoxon were used to validate the new AChE assay method. AChE inhibition in OP dosed solutions was proportional to OP concentration from 0.2 to 50 nM. The new AChE activity assay method for biomonitoring of OP exposure was further validated with in vitro paraoxon-dosed RBC samples. The established electrochemical sensing platform for AChE activity assay not only avoids the problem of overlapping substrate specificity with esterases by using selective antibody, but also eliminates potential interference from other electroactive species in biological samples. It offers a new approach for sensitive, selective, and rapid AChE activity assay for biomonitoring of exposure to OPs.

Status
MEDLINE
Institution
Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China.

Integrated lateral flow test strip with electrochemical sensor for quantification of phosphorylated cholinesterase: biomarker of exposure to organophosphorus agents.
Du D.  Wang J.  Wang L.  Lu D.  Lin Y.
Analytical Chemistry.  84(3):1380-5, 2012 Feb 7.
UI: 22243414
An integrated lateral flow test strip with an electrochemical sensor (LFTSES) device with rapid, selective, and sensitive response for quantification of exposure to organophosphorus (OP) pesticides and nerve agents has been developed. The principle of this approach is based on parallel measurements of postexposure and baseline acetylcholinesterase (AChE) enzyme activity, where reactivation of the phosphorylated AChE is exploited to enable measurement of the total amount of AChE (including inhibited and active) which is used as a baseline for calculation of AChE inhibition. Quantitative measurement of phosphorylated adduct (OP-AChE) was realized by subtracting the active AChE from the total amount of AChE. The proposed LFTSES device integrates immunochromatographic test strip technology with electrochemical measurement using a disposable screen printed electrode which is located under the test zone. It shows a linear response between AChE enzyme activity and enzyme concentration from 0.05 to 10 nM, with a detection limit of 0.02 nM. On the basis of this reactivation approach, the LFTSES device has been successfully applied for in vitro red blood cells inhibition studies using chlorpyrifos oxon as a model OP agent. This approach not only eliminates the difficulty in screening of low-dose OP exposure because of individual variation of normal AChE values but
also avoids the problem in overlapping substrate specificity with cholinesterases and avoids potential interference from other electroactive species in biological samples. It is baseline free and thus provides a rapid, sensitive, selective, and inexpensive tool for in-field and point-of-care assessment of exposures to OP pesticides and nerve agents. 2011 American Chemical Society Status

MEDLINE
Institution
Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China. dudan@mail.ccnu.edu.cn

10. Preparation, characterization of Fe3O4 at TiO2 magnetic nanoparticles and their application for immunoassay of biomarker of exposure to organophosphorus pesticides.
Zhang X. Wang H. Yang C. Du D. Lin Y.
[Journal Article. Research Support, N.I.H., Extramural. Research Support, Non-U.S. Gov't]
UI: 23122753
Novel Fe(3)O(4) at TiO(2) magnetic nanoparticles were prepared and developed for a new nanoparticle-based immunosensor for electrochemical quantification of organophosphorylated butyrylcholinesterase (BChE) in plasma, a specific biomarker of exposure to organophosphorus (OP) agents. The Fe(3)O(4) at TiO(2) nanoparticles were synthesized by hydrolysis of tetrabutyltitanate on the surface of Fe(3)O(4) magnetic nanospheres, and characterized by attenuated total reflection Fourier-transform infrared spectra, transmission electron microscope and X-ray diffraction. The functional Fe(3)O(4) at TiO(2) nanoparticles were performed as capture antibody to selectively enrich phosphorylated moiety instead of phosphoserine antibody in the traditional sandwich immunoassays. The secondary recognition was performed by quantum dots (QDs)-tagged anti-BChE antibody (QDs-anti-BChE). With the help of a magnet, the resulting sandwich-like complex, Fe(3)O(4) at TiO(2)/OP-BChE/QDs-anti-BChE, was easily isolated from sample solutions and the released cadmium ions were detected on a disposable screen-printed electrode (SPE). The binding affinities were investigated by both surface plasmon resonance (SPR) and square wave voltammetry (SWV). This method not only avoids the drawback of unavailability of commercial OP-specific antibody but also amplifies detection signal by QDs-tags together with easy separation of samples by magnetic forces. The proposed immunosensor yields a linear response over a broad OP-BChE concentrations range from 0.02 to 10 nM, with
detection limit of 0.01 nM. Moreover, the disposable nanoparticle-based immunosensor has been validated with human plasma samples. It offers a new method for rapid, sensitive, selective and inexpensive screening/evaluating exposure to OP pesticides and nerve agents. Copyright 2012 Elsevier B.V. All rights reserved.

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Institution
Key Laboratory of Pesticide and Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China.

11. Immunodetection of serum albumin adducts as biomarkers for organophosphorus exposure. Chen S. Zhang J. Lumley L. Cashman JR.
[Journal Article. Research Support, N.I.H., Extramural]
UI: 23192655
A major challenge in organophosphate (OP) research has been the identification and utilization of reliable biomarkers for the rapid, sensitive, and efficient detection of OP exposure. Although Tyr 411 OP adducts to human serum albumin (HSA) have been suggested to be one of the most robust biomarkers in the detection of OP exposure, the analysis of HSA-OP adduct detection has been limited to techniques using mass spectrometry. Herein, we describe the procurement of two monoclonal antibodies (mAb-HSA-GD and mAb-HSA-VX) that recognized the HSA Tyr 411 adduct of soman (GD) or S-[2-(diisopropylamino)ethyl]-O-ethyl methylphosphonothioate (VX), respectively, but did not recognize nonphosphonylated HSA. We showed that mAb-HSA-GD was able to detect the HSA Tyr 411 OP adduct at a low level (i.e., human blood plasma treated with 180 nM GD) that could not be detected by mass spectrometry. mAb-HSA-GD and mAb-HSA-VX showed an extremely low-level detection of GD adducted to HSA (on the order of picograms). mAb-HSA-GD could also detect serum albumin OP adducts in blood plasma samples from different animals administered GD, including rats, guinea pigs, and monkeys. The ability of the two antibodies to selectively recognize nerve agents adducted to serum albumin suggests that these antibodies could be used to identify biomarkers of OP exposure and provide a new biologic approach to detect OP exposure in animals.

Status
MEDLINE
Institution
Evaluation of the tear and serum levels of IL-8 in sulfur mustard intoxicated patients 20 years after exposure.

Ghasemi H. Ghazanfari T. Yaraee R. Pourfarzam S. Soroush MR. Faghihzadeh S. Babaei M. Naghizadeh MM. Mohammad Hassan Z.


[Journal Article. Research Support, Non-U.S. Gov't]

UI: 21967620

PURPOSE: Delayed keratitis is the most dangerous ocular complication of sulfur mustard (SM) exposure. This study aimed to evaluate the role of tear and serum levels of interleukin-8 (IL-8) in SM exposed subjects.

DESIGN AND METHODS: In this historical cohort study, the experimental group included 370 participants who had been exposed to SM 20 years prior. Data were compared with those of 128 unexposed participants as the control group. After completing a thorough systemic and ocular examination, serum IL-8 levels in all exposed and controls were compared. According to the statistical calculation, tear IL-8 levels, were compared in randomly selected 48 exposed and 37 controls. Based on the ocular findings, the selected subjects were divided into two subgroups, normal subjects include those participants who had no ocular signs and abnormal subjects, were those who had at least one or more ocular signs.

RESULTS: Bulbar conjunctiva and limbal tissues evaluation in all participants showed a significantly higher number of abnormalities in exposed group than in the control group (P=0.004 and P=0.048 respectively). Serum IL-8 levels in all exposed were significantly lower than the matched controls (P=0.002). Tear IL-8 levels in the selected exposed were significantly lower than in the selected controls (P=0.030). In exposed group with normal conditions of the lids, bulbar conjunctiva, cornea, tear status, limbus, slit lamp findings and final ophthalmic assessment, tear IL-8 levels were significantly lower than in the matched controls (P=0.022, 0.037, 0.027, 0.050, 0.039, 0.029, 0.045 respectively). With respect to the global ophthalmic assessment, tear fluid IL-8 levels in the abnormal controls were significantly lower than in the normal controls (P=0.049), but this decrease in secretion of tear IL-8 were not encountered in abnormal exposed (P=0.415).

CONCLUSION: Tear IL-8 secretion was significantly inhibited in the
A 10-minute point-of-care assay for detection of blood protein adducts resulting from low level exposure to organophosphate nerve agents.


UI: 23200942

The OrganoTox test is a rapid, point-of-care assay capable of detecting clinically relevant organophosphate (OP) poisoning after low-level exposure to sarin, soman, tabun, or VX chemical nerve agents. The test utilizes either a finger stick peripheral blood sample or plasma specimen. While high-level nerve agent exposure can quickly lead to death, low-level exposure produces vague, nondescript signs and symptoms that are not easily clinically differentiated from other conditions. In initial testing, the OrganoTox test was used to detect the presence of blood protein-nerve agent adducts in exposed blood samples. In order to mimic the in vivo exposure as closely as possible, nerve agents stored in organic solvents were spiked in minute quantities into whole blood samples. For performance testing, 40 plasma samples were spiked with sarin, soman, tabun, or VX and 10 normal plasma samples were used as the negative control. The 40 nerve agent-spiked plasma samples included 10 replicates of each agent. At the clinically relevant low-level exposure of 10 ng/ml, the OrganoTox test demonstrated 100% sensitivity for soman, tabun, and VX and 80% sensitivity for sarin. The OrganoTox test demonstrated greater than 97% specificity with 150 blood samples obtained from healthy adults. No cross-reactivity or interference from pesticide precursor compounds was found. A rapid test for nerve agent exposure will help identify affected patients earlier in the clinical course and trigger more appropriate medical management in a more timely manner. Copyright 2012 Elsevier Ireland Ltd. All rights reserved.

Status
MEDLINE
Institution
Rapid Pathogen Screening, 7227 Delainey Court, Sarasota, FL 34240, USA.

14.

Transcriptional responses of the nerve agent-sensitive brain regions amygdala, hippocampus, piriform cortex, septum, and thalamus following exposure to the organophosphonate anticholinesterase sarin.


UI: 21777430

BACKGROUND: Although the acute toxicity of organophosphorus nerve agents is known to result from acetylcholinesterase inhibition, the molecular mechanisms involved in the development of neuropathology following nerve agent-induced seizure are not well understood. To help determine these pathways, we previously used microarray analysis to identify gene expression changes in the rat piriform cortex, a region of the rat brain sensitive to nerve agent exposure, over a 24-h time period following sarin-induced seizure. We found significant differences in gene expression profiles and identified secondary responses that potentially lead to brain injury and cell death. To advance our understanding of the molecular mechanisms involved in sarin-induced toxicity, we analyzed gene expression changes in four other areas of the rat brain known to be affected by nerve agent-induced seizure (amygdala, hippocampus, septum, and thalamus).

METHODS: We compared the transcriptional response of these four brain regions to sarin-induced seizure with the response previously characterized in the piriform cortex. In this study, rats were challenged with 1.0 x LD50 sarin and subsequently treated with atropine sulfate, 2-pyridine aldoxime methylchloride, and diazepam. The four brain regions were collected at 0.25, 1, 3, 6, and 24 h after seizure onset, and total RNA was processed for microarray analysis.

RESULTS: Principal component analysis identified brain region and time following seizure onset as major sources of variability within the dataset. Analysis of variance identified genes significantly changed following sarin-induced seizure, and gene ontology analysis identified biological pathways, functions, and networks of genes significantly affected by sarin-induced seizure over the 24-h time course. Many of the molecular functions and pathways identified as being most significant across all of the brain regions were indicative of an inflammatory response. There were also a number of molecular responses that were unique for each brain region, with the thalamus having the most distinct response to nerve agent-induced seizure.

CONCLUSIONS: Identifying the molecular mechanisms involved in sarin-induced neurotoxicity in these sensitive brain regions will facilitate the development of novel therapeutics that can
potentially provide broad-spectrum protection in five areas of the central nervous system known
to be damaged by nerve agent-induced seizure.

Status
MEDLINE
Institution
Cell and Molecular Biology Branch, US Army Medical Research Institute of Chemical Defense
(USAMRICD), 3100 Ricketts Point Road, Aberdeen Proving Ground, MD 21010-5400, USA.

15.
Repeated exposure to sublethal doses of the organophosphorus compound VX activates BDNF
expression in mouse brain.

Pizarro JM. Chang WE. Bah MJ. Wright LK. Saviolakis GA. Alagappan A. Robison CL. Shah
JD. Meyerhoff JL. Cerasoli DM. Midboe EG. Lumley LA.
[Journal Article. Research Support, Non-U.S. Gov't]
UI: 22240983

The highly toxic organophosphorus compound VX [O-ethyl S-[2-(diisopropylamino)ethyl]methylphosphonate] is an irreversible inhibitor of the enzyme
acetylcholinesterase (AChE). Prolonged inhibition of AChE increases endogenous levels of
acetylcholine and is toxic at nerve synapses and neuromuscular junctions. We hypothesized that
repeated exposure to sublethal doses of VX would affect genes associated with cell survival,
neuronal plasticity, and neuronal remodeling, including brain-derived neurotrophic factor (BDNF).
We examined the time course of BDNF expression in C57BL/6 mouse brain following repeated
exposure (1/day x 5 days/week x 2 weeks) to sublethal doses of VX (0.2 LD(50) and 0.4 LD(50)).
BDNF messenger RNA expression was significantly (p < 0.05) elevated in multiple brain regions,
including the dentate gyrus, CA3, and CA1 regions of the hippocampal formation, as well as the
piriform cortex, hypothalamus, amygdala, and thalamus, 72 h after the last 0.4 LD(50) VX
exposure. BDNF protein expression, however, was only increased in the CA3 region of the
hippocampus. Whether increased BDNF in response to sublethal doses of VX exposure is an
adaptive response to prevent cellular damage or a precursor to impending brain damage remains
to be determined. If elevated BDNF is an adaptive response, exogenous BDNF may be a
potential therapeutic target to reduce the toxic effects of nerve agent exposure.

Status
16. Safety of administration of human butyrylcholinesterase and its conjugates with soman or VX in rats.
Genovese RF. Sun W. Johnson CC. Ditargiani RC. Doctor BP. Saxena A.
Basic & Clinical Pharmacology & Toxicology. 106(5):428-34, 2010 May.
[Journal Article. Research Support, U.S. Gov't, Non-P.H.S.]
UI: 20050840
We evaluated the effects of conjugated enzyme-nerve agent product resulting from the inhibition of bioscavenger human serum butyrylcholinesterase (Hu BChE) by nerve agents soman or VX. Rats were trained on a multiple Fixed-Ratio 32, Extinction 30 sec. (FR32, Ext30) schedule of food reinforcement and then injected (i.m.) with Hu BChE (30 mg/kg), equivalent amounts of Hu BChE-soman conjugate (GDC), Hu BChE-VX conjugate, oxotremorine (OXO) (0.316 mg/kg) or vehicle (n = 8, each group). On the day of injection and on 10 subsequent daily sessions, performance was evaluated on the FR32, Ext30 schedule. Neither conjugates nor Hu BChE produced a performance deficit under the schedule. OXO produced a substantial decrease in responding on the day of administration, with complete recovery observed on subsequent sessions. None of the treatments affected circulating acetylcholinesterase (AChE) activity when evaluated 24-72 hr after injection. The dose of Hu BChE produced a 20,000-fold increase above baseline in circulating BChE activity. Pathological evaluation of organ systems approximately 2 weeks following administration of conjugates or Hu BChE alone did not show toxicity. Taken together, these results suggest that Hu BChE - nerve agent conjugates produced following bioscavenger protection against nerve agents soman and VX do not appear to be particularly toxic. These results add to the safety assessment of Hu BChE as a bioscavenger countermeasure against nerve agent exposure.
Status
MEDLINE
Institution