28 January 2010

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Chem-Bio News – S&T Edition

1. EFFECTS OF 4-PYRIDINE ALDOXIME ON NERVE AGENT-INHIBITED ACETYLCHOLINESTERASE ACTIVITY IN GUINEA PIGS: *"There is a possibility that 4-PA may adversely interact with the nerve agent, thereby affecting nerve agent toxicity and biological AChE activity."*

2. EFFECTIVENESS OF DONEPEZIL, RIVASTIGMINE, AND (+/-)HUPERZINE A IN COUNTERACTING THE ACUTE TOXICITY OF ORGANOPHOSPHORUS NERVE AGENTS: COMPARISON WITH GALANTAMINE: *"Thus, galantamine emerges as a superior antidotal therapy against the toxicity of soman."*

3. A VENUS FLYTRAP FOR NUCLEAR WASTE: *"It is, in fact, cesium itself that triggers a structural change in the material, causing it to snap shut its pores, or windows, and trap the cesium ions within. The material sequesters 100 percent of the cesium ions from the solution while at the same time ignoring all the sodium ions."*

4. NEURON ARRAY ADVANCES TOXICITY TESTING: *"Scientists in Germany have developed an alternative to animal testing for rapid screening and identification of chemicals that pose a health risk to the human nervous system."*

5. INTERACTION BETWEEN EBOLA VIRUS GLYCOPROTEIN AND HOST TOLL-LIKE RECEPTOR 4 LEADS TO INDUCTION OF PROINFLAMMATORY CYTOKINES AND SOCS1: *"In sum, these findings identify the host innate immune protein TLR4 as a sensor for Ebola virus GP which may play an important role in the immunopathogenesis of Ebola virus infection."*

6. RICIN A-CHAIN REQUIRES C-JUN N-TERMINAL KINASE TO INDUCE APOPTOSIS IN NONTRANSFORMED EPITHELIAL CELLS: *"In addition, the MAC-T cell line is shown to be a sensitive in vitro model system for future studies using RTA mutants to determine relationships between RTA-induced depurination, ribotoxic stress, and apoptosis in normal epithelial cells."*

CB Daily Report

Chem-Bio News

EFFECTS OF 4-PYRIDINE ALDOXIME ON NERVE AGENT-INHIBITED ACETYLCHOLINESTERASE ACTIVITY IN GUINEA PIGS
Drug Week
January 22, 2010

"Methoxime (MMB-4) is a leading candidate oxime acetylcholinesterase (AChE) reactivator to replace pralidoxime (2-PAM) for therapeutic treatment of nerve agent intoxication. 4-Pyridine aldoxime (4-PA) is a synthetic starting material, a breakdown product, and a probable metabolite of MMB-4. There is a possibility that 4-PA may adversely interact with the nerve agent, thereby affecting nerve agent toxicity and biological AChE activity."

"This study evaluated the effects of 4-PA on sarin (GB)-, cyclosarin (GF)-, and VX-induced toxicity and AChE activity in blood, brain, and peripheral tissues of guinea pigs. Animals were pretreated with atropine methyl nitrate (1.0 mg/kg, im) 15 min prior to subcutaneous administration with 1.0x LD50 of GB, GF, or VX and then treated 15 min after the administration of nerve agents with 4-PA (3.5, 7.0, or 14.0 mg/kg, im). The dose-response effects of 4-PA alone were also examined. Toxic signs and lethality were monitored, blood and tissues were collected, and AChE activities were determined at 60 min after nerve agent administration. Under the condition of this study, all animals exposed to nerve agents exhibited some degree of toxic signs such as salivation, lacrimation, rhinorrhea, and convulsions. 4-PA at the three doses tested neither induced toxic signs nor altered the toxicity of GB, GF, or VX at the 1.0x LD50 exposure dose."

"Additionally, it did not modify the AChE activity in blood, brain, and peripheral tissues by itself or affect the AChE activity inhibited by a 1.0x LD50 dose of these three nerve agents in guinea pigs."

The full article can be found at: (T.M. Shih, et. al., "Effects of 4-pyridine aldoxime on nerve agent-inhibited acetylcholinesterase activity in guinea pigs". Archives of Toxicology, 2009;83 (12):1083-1089). Link not available.

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EFFECTIVENESS OF DONEPEZIL, RIVASTIGMINE, AND (+/-)HUPERZINE A IN COUNTERACTING THE ACUTE TOXICITY OF ORGANOPHOSPHORUS NERVE AGENTS: COMPARISON WITH GALANTAMINE
Drug Week
January 29, 2010

"Galantamine, a centrally acting cholinesterase (ChE) inhibitor and a nicotinic allosteric potentiating ligand used to treat Alzheimer's disease, is an effective and safe antidote against poisoning with nerve agents, including soman. Here, the effectiveness of galantamine was compared with that of the centrally active ChE inhibitors donepezil,

rivastigmine, and (+/-)huperzine A as a pre- and/or post-treatment to counteract the acute toxicity of soman."

"In the first set of experiments, male prepubertal guinea pigs were treated intramuscularly with one of the test drugs and 30 min later challenged with 1.5 x LD50 soman (42 mu g/kg s.c.). All animals that were pretreated with galantamine (6-8 mg/kg), 3 mg/kg donepezil, 6 mg/kg rivastigmine, or 0.3 mg/kg (+/-)huperzine A survived the soman challenge, provided that they were also post-treated with atropine (10 mg/kg i.m.). However, only galantamine was well tolerated. In subsequent experiments, the effectiveness of specific treatment regimens using 8 mg/kg galantamine, 3 mg/kg donepezil, 6 mg/kg rivastigmine, or 0.3 mg/kg (+/-)huperzine A was compared in guinea pigs challenged with soman. In the absence of atropine, only galantamine worked as an effective and safe pretreatment in animals challenged with 1.0 x LD50 soman. Galantamine was also the only drug to afford significant protection when given to guinea pigs after 1.0 x LD50 soman. Finally, all test drugs except galantamine reduced the survival of the animals when administered 1 or 3 h after the challenge with 0.6 or 0.7 x LD50 soman."

"Thus, galantamine emerges as a superior antidotal therapy against the toxicity of soman."

The full article can be found at: (Y. Aracava, et. al., "Effectiveness of Donepezil, Rivastigmine, and (+/-)Huperzine A in Counteracting the Acute Toxicity of Organophosphorus Nerve Agents: Comparison with Galantamine". Journal of Pharmacology and Experimental Therapeutics, 2009;331(3):1014-1024). Link not available.

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A VENUS FLYTRAP FOR NUCLEAR WASTE
Physorg.com
January 26, 2010

"The synthetic material, made from layers of a gallium, sulfur and antimony compound, is very selective. The Northwestern researchers found it to be extremely successful in removing cesium -- found in nuclear waste but very difficult to clean up -- from a sodium-heavy solution. (The solution had concentrations similar to those in real liquid nuclear waste.)

It is, in fact, cesium itself that triggers a structural change in the material, causing it to snap shut its pores, or windows, and trap the cesium ions within. The material sequesters 100 percent of the cesium ions from the solution while at the same time ignoring all the sodium ions.

The results are published online by the journal Nature Chemistry.

"Ideally we want to concentrate the radioactive material so it can be dealt with properly and the nonradioactive water thrown away," said Mercouri G. Kanatzidis, Charles E. and Emma H. Morrison Professor of Chemistry in the Weinberg College of Arts and Sciences and the paper's senior author. "A new class of materials that takes advantage of the flytrap

mechanism could lead to a much-needed breakthrough in nuclear waste remediation."

Capturing only cesium from vast amounts of liquid nuclear waste is like looking for a needle in a haystack, Kanatzidis said. The waste has a much higher concentration of sodium compared to cesium, with ratios as great as 1,000-to-1. This difficult-to-achieve selectivity is why currently there is no good solution for cesium removal."

The full article can be found at: http://www.physorg.com/news183749230.html

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NEURON ARRAY ADVANCES TOXICITY TESTING
By Janet Crombie
Highlights in Chemical Technology
January 25, 2010

"Their new testing platform, called a network formation assay (NFA), monitors connections (or outgrowths) between specifically placed neurons and their neighbours. The formation of these connections is one of the basic principles of memory and learning, and its disturbance is frequently a clinical sign of neurotoxicity, says West. 'Because NFA examines neuron connections it represents an in vitro model that is comparable to the in vivo state', he adds.

West placed human neurons within a hexagonal array using cell patterning and could then easily monitor the formation of the network. Exposing the array to acrylamide, a neurotoxic reference compound inhibited network formation and distinguished between neurotoxic and cytotoxic effects. Without the need to locate the neurons or measure the lengths of the connections, means that a typical assay takes only three hours compared with up to 200 hours for manual testing."

The full article can be found at: http://www.rsc.org/Publishing/ChemTech/Volume/2010/02/Invitro_array.asp

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INTERACTION BETWEEN EBOLA VIRUS GLYCOPROTEIN AND HOST TOLL-LIKE RECEPTOR 4 LEADS TO INDUCTION OF PROINFLAMMATORY CYTOKINES AND SOCS1
Blood Weekly
February 4, 2010

"According to recent research from the United States, "Ebola virus initially targets monocytes and macrophages, which can lead to the release of proinflammatory cytokines and chemokines. These inflammatory cytokines are thought to contribute to the development of circulatory shock seen in fatal Ebola virus infections."

"Here we report that host Toll-like receptor 4 (TLR4) is a sensor for Ebola virus glycoprotein

(GP) on virus-like particles (VLPs) and that resultant TLR4 signaling pathways lead to the production of proinflammatory cytokines and suppressor of cytokine signaling 1 (SOCS1) in a human monocytic cell line and in HEK293-TLR4/MD2 cells stably expressing the TLR4/MD2 complex. Ebola virus GP was found to interact with TLR4 by immunoprecipitation/Western blot analyses, and Ebola virus GP on VLPs was able to stimulate expression of NF-kappaB in a TLR4-dependent manner. Interestingly, we found that budding of Ebola virus VLPs was more pronounced in TLR4-stimulated cells than in unstimulated control cells."

"In sum, these findings identify the host innate immune protein TLR4 as a sensor for Ebola virus GP which may play an important role in the immunopathogenesis of Ebola virus infection."

The full article can be found at: (A. Okumura, et. al., "Interaction between Ebola virus glycoprotein and host toll-like receptor 4 leads to induction of proinflammatory cytokines and SOCS1". Journal of Virology, 2010;84(1):27-33). Link not available.

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RICIN A-CHAIN REQUIRES C-JUN N-TERMINAL KINASE TO INDUCE APOPTOSIS IN NONTRANSFORMED EPITHELIAL CELLS
Biotech Week
January 27, 2010

"Ricin is a toxin isolated from castor beans that has potential as a weapon of bioterrorism. This glycoprotein consists of an A-chain (RTA) that damages the ribosome and inhibits protein synthesis and a B-chain that plays a role in cellular uptake."

"Ricin activates the c-Jun N-terminal kinase (JNK) and p38 signaling pathways; however, a role for these pathways in ricin-induced cell death has not been investigated. Our goals were to determine if RTA alone could activate apoptosis and if the JNK and p38 pathways were required for this response. Comparable caspase activation was observed with both ricin and RTA treatment in the immortalized, nontransformed epithelial cell line, MAC-T. Ribosome depurination and inhibition of protein synthesis were induced in 2-4 h with 1 mu g/ml RTA and within 4-6 h with 0.1 mu g/ml RTA. Apoptosis was not observed until 4h of treatment with either RTA concentration. RTA activated JNK and p38 in a time- and concentration-dependent manner that preceded increases in apoptosis. Inhibition of the JNK pathway reduced RTA-induced caspase activation and poly(ADP-ribose) polymerase cleavage. In contrast, inhibition of the p38 pathway had little effect on RTA-induced caspase 3/7 activation. These studies are the first to demonstrate a role for the JNK signaling pathway in ricin-induced cell death."

"In addition, the MAC-T cell line is shown to be a sensitive in vitro model system for future studies using RTA mutants to determine relationships between RTA-induced depurination, ribotoxic stress, and apoptosis in normal epithelial cells."

The full article can be found at: (A.E. Jetzt, et. al., "Ricin A-chain requires c-Jun N-terminal kinase to induce apoptosis in nontransformed epithelial cells". International Journal of

Biochemistry & Cell Biology, 2009;41(12):2503-2510). Link not available.

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