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Mechanisms of action of additive stimuli

2005-09-08

Drug addiction and multiple chemical intolerance (abdiction) appear to be polar opposites, the former characterized by craving and dependency, the latter by aversion. However, when the two are viewed in juxtaposition similarities emerge, revealing a common underlying dynamic, one which appears to be a new paradigm of disease. TILT, or toxicant-induced loss of tolerance, bridges the gap between addiction and abdiction and has the potential to explain a variety of illnesses, including certain cases of asthma, migraine headaches and depression, as well as chronic fatigue syndrome, bromyalgia and Gulf War syndrome. This paper argues that both addiction and chemical intolerance involve a fundamental breakdown in innate tolerance, resulting in an amplification of various biological effects, particularly withdrawal symptoms. While addicts seek further exposures so as to avoid unpleasant withdrawal symptoms, chemically intolerant individuals shun their problem exposures, but for the same reason to avoid unpleasant withdrawal symptoms.

These observations raise critical questions: do addictive drugs and environmental pollutants initiate an identical disease process? Once this process begins, can both addictants and pollutants trigger symptoms and cravings? Evidence from more than a dozen countries suggests that certain, presumably more susceptible, individuals develop chemical, food, alcohol, caffeine, and drug intolerances following an identifiable environmental exposure event, e.g., to solvents, pesticides, indoor air contaminants and other environmental toxicants. Subsequently, affected individuals responses to everyday inhalants and ingestants bear a striking resemblance to those observed in drug and alcohol addiction, including debilitating multi-system symptoms especially CNS symptoms, intolerances for structurally unrelated substances (paralleling cross-addiction), stimulatory and withdrawal symptoms, and cravings. Drug addiction and chemical intolerance (or abdiction moving away from the substance) appear to share a common underlying dynamic, one that suggests a new disease paradigm that has been called Toxicant-induced loss of tolerance in the field of environmental health. Toxicant-induced loss of tolerance (TILT) appears to bridge the gap between addiction and abdiction and may help explain a wide variety of chronic illnesses.

Authors: Claudia S. Miller
Full source: Addiction (2000) 96(1), 115"139

Acute selenium poisoning: Suicide by ingestion

2005-09-08

Selenium is a ubiquitous element in the environment essential to the human diet and widely utilized in industrial processes. Fatal human selenium intoxication is rare. The authors report a case in which investigators recovered a bottle of gun-bluing agent beside a 24-year-old man. He exhibited signs and symptoms typical of acute selenium intoxication presenting with nausea and vomiting, followed by pulmonary edema and rapid cardiovascular collapse approximately 3 to 4 h after ingestion. Classic electrocardiogram (ECG) changes, which have been reported to occur in acute selenium intoxication, included sinus tachycardia with ST wave alteration. Toxicological results confirmed elevated blood and tissue concentrations. The cause of death was ascribed to acute selenium intoxication, which ensued rapidly after oral consumption. The manner of death was suicide. This case report, which presents an overview of acute and chronic selenium poisoning, underscores the value of thorough toxicological analyses of tissue and body fluids in humans.
The advent of the industrial revolution has seen a significant increase in the number of new chemical entities (NCEs) released in the environment. It becomes imperative to check the toxic potential of NCEs to nontarget species before they are released for commercial purposes because some of these may exert genotoxicity, mutagenicity, or carcinogenicity. Exposure to such compounds produces chemical changes in DNA, which are generally repaired by the DNA repair enzymes. However, DNA damage and its fixation may occur in the form of gene mutations, chromosomal damage, and numerical chromosomal changes and recombination. This may affect the incidence of heritable mutations in man and may be transferred to the progeny or lead to the development of cancer. Hence, adequate tests on NCEs have to be undertaken for the risk assessment and hazard prediction. Compounds that are positive in tests that detect such damages have the potential to be human mutagens/carcinogens. Only long-term animal bioassays, involving lifetime studies on animals, were used earlier to classify substances as mutagens/carcinogens. These tests were cumbersome and time consuming and required a lot of facilities and personnel. Short-term tests, therefore, were brought into practice. A “battery” of three to four of these short-term tests has been proposed now by a number of regulatory authorities for the classification of compounds as mutagenic or carcinogenic. This review deals with the current status of these short-term tests.

In situ naphthalene bioactivation and nasal airflow cause region-specific injury patterns in the nasal mucosa of rats exposed to naphthalene by inhalation

Despite the fact that naphthalene (NA), a volatile, ubiquitous air pollutant, was recently identified as a probable human carcinogen, little is known about nasal cytotoxicity from inhaled NA. To define and compare acute nasal injury from inhalation and systemic NA exposures, male Sprague-Dawley rats were exposed to filtered air; 3.4 or 23.8 ppm NA by inhalation for 4 h; or to 0, 25, 50, 100, or 200 mg/kg NA via i.p. injection. Severe cellular injury occurred exclusively in the olfactory mucosa 24 h postinhalation exposure to 3.4 ppm NA for 4 h. This level is significantly below both the current Occupational Safety and Health Administration standard (10 ppm; 8 h) for NA and the lowest observed adverse effect level (10 ppm; 2 years) for the incidence of rat olfactory neoplasms. Injury within the olfactory mucosa from inhaled NA was confined to the medial meatus, whereas systemic NA generated severe injury throughout the olfactory region. The pattern of nasal injury from inhaled NA in this study is consistent with previous studies of nasal airflow simulation within the olfactory region. The nonolfactory mucosa on the nasal septum, a high airflow region, metabolized naphthalene slowly, whereas the olfactory regions of the nasal septum and ethmoturbinates metabolized this substrate at high rates. This study concludes that 1) the...
The effects of 1-month administration of asoprisnil (J867), a selective progesterone receptor modulator, in healthy premenopausal women
2005-09-08
Asoprisnil (J867) is a novel selective progesterone receptor modulator (SPRM) that exhibits partial agonist and antagonist activities and tissue selective effects. This double-blind, dose-escalation study was conducted to evaluate the effects of asoprisnil in 60 regularly cycling premenopausal women. Asoprisnil consistently prolonged the menstrual cycle at doses >=10 mg QD. However, the effects on luteal phase progesterone indicative of luteinization were inconsistent and lacked dose dependency. Asoprisnil suppressed periovulatory estradiol but not below follicular phase levels. No significant changes were observed in cortisol and prolactin. Asoprisnil was well tolerated. Asoprisnil reversibly suppressed menstruation at doses >=10 mg QD irrespective of the effect on luteal phase progesterone concentrations indicative of luteinization. It induces amenorrhea primarily by targeting the endometrium in the absence of estrogen deprivation.
Authors: Chwalisz, Kristof; Elger, Walter; Stickler, Therese; Mattia-Goldberg, Cynthia; Larsen, Lois

The future of teratology research is in vitro
2005-09-08
Birth defects induced by maternal exposure to exogenous agents during pregnancy are preventable, if the agents themselves can be identified and avoided. Billions of dollars and man-hours were dedicated to animal-based discovery and characterization methods over decades. Authors show here, via a comprehensive systematic review and analysis of this data, that these methods constitute questionable science and pose a hazard to humans. Mean positive and negative predictivities barely exceed 50%; discordance among the species used is substantial; reliable extrapolation from animal data to humans is impossible, and virtually all known human teratogens have so far been identified in spite of, rather than because of, animal-based methods. Despite strict validation criteria that animal-based teratology studies would fail to meet, 3 in vitro alternatives have done so. The embryonic stem-cell test (EST) is the best of these. Authors argue that the poor performance of animal-based teratology alone warrants its cessation; it ought to be replaced by the easier, cheaper and more repeatable EST, and resources made available to improve this and other tests even further.
Authors: Bailey, Jarrod; Knight, Andrew; Balcombe, Jonathan
Full source: Biogenic Amines 2005, 19(2), 97-145 (Eng)

Comparison of inductively coupled plasma mass spectrometry techniques in the determination of platinum in urine: Quadrupole versus Sector field
2005-09-08
In recent years the increasing use of platinum (Pt) both in medical and

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in industrial applications has caused its growing anthropogenic emission and spread in the environment. Pt is released into the atmosphere by exhaust catalytic converters, and Pt compounds are often used in antitumor therapies. As a consequence, significant amounts of Pt can be detected in hospital wastewaters. This can lead to an increase in the exposure levels to Pt, especially in urban areas. It is therefore necessary to determine Pt reference values in the general population, by using suitable procedures able to achieve adequate analysis performances. The present paper considers the measurement of urinary Pt levels in a general population group from central Italy, by both quadrupole (Q) and sector field (SF) inductively coupled plasma mass spectrometry (ICP-MS). The limits of detection (LODs), calculated taking into account dilution factors, were 0.18 and 0.05 ng L⁻¹ of Pt for the Q and SF procedures, respectively. The median value observed was 4.13 ng L⁻¹ of Pt in urine, while the relative combined uncertainty at 5 ng L⁻¹ was below 20% with both ICP-MS techniques. These data are in good agreement with those reported in the literature for similar studies.

Authors: Spezia, Sandro; Bocca, Beatrice; Forte, Giovanni; Gatti, Anna; Mincione, Giovanna; Ronchi, Anna; Bavazzano, Paolo; Alimonti, Alessandro; Minoa, Claudio

Full source: Rapid Communications in Mass Spectrometry 2005, 19(11), 1551-1556 (Eng)

Effects of chronic lead exposure on 1H MRS of hippocampus and frontal lobes in children
2005-09-08
The authors performed IQ testing and magnetic resonance spectroscopy on 6 Pb-exposed and 6 control children. Levels of N-acetyl aspartate (neuronal density and mitochondrial metabolism), creatine + phosphocreatine (phosphate metabolism), and choline (membrane turnover) were decreased in 4 brain regions (left and right frontal, left and right hippocampus) in Pb-exposed children versus controls. The reductions were right frontal > left frontal > hippocampus but were the same bilaterally in the hippocampus.

Authors: Meng, X.-M.; Zhu, D.-M.; Ruan, D.-Y.; She, J.-Q.; Luo, L.

Full source: Neurology 2005, 64(9), 1644-1647 (Eng)

Safety evaluation of tobacco substitute (Herbrette); inhalation toxicity, mutagenicity and immunotoxicity
2005-09-08
Inhalation toxicity, mutagenicity, and immunotoxicity tests were performed using a smoke generation system to investigate the safety of Herbrette, a tobacco substitute made with the leaves of Perilla frutescens. ICR mice were exposed to nicotine-free Herbrette smoke with concentrations of 0 (control), 4.08 ± 1.32 mg/m³ (low dose), 7.72 ± 2.14 mg/m³ (medium dose) and 12.83 ± 1.69 mg/m³ (high dose) total particulate matters (TPM) for 4 weeks. When compared to the control group, the body weights, organ weights in the exposed groups did not show any significant differences. However, certain change of several serum chemical data and biochemical parameters were observed, however, the changes were within normal physiological ranges. Moreover, no changes in organ weight, and no gross/microscopic changes were observed between the exposed and control groups. Salmonella typhimurium reverse mutation, in vivo chromosomal aberration and micronucleus assays revealed that Herbrette did not induce mutagenicity. Upon evaluation of peripheral cellular immunity of mice through in vitro lymphocyte proliferation assay, no significant difference was observed in mean stimulation index between the exposed and control groups. Taken together, these results strongly suggest
that Herbrette may not cause toxicity on mice under current condition.
Authors: Song, Kyung Seuk; Park, Kun Ho; Yoo, Gi Yong; Song, Sung-Ok; Kim, Hyun Woo; Kim, Jun Sung; Park, Jin Hong; Eu, Guk Joung; Hua, Jin; Cho, Hyun Sun; Hwang, Soon Kyung; Chang, Seung Hee; Tehrani, Arash Minai; Yu, Kyeong Nam; Chae, Chan Hee; Cho, Myung Haing
Full source: Journal of Toxicology and Public Health 2004, 20(4), 365-374 (Eng)

Effects of long-term occupational solvent exposure on contrast sensitivity and performance in visual search
2005-09-08
Sensitive, easily applicable screening tests are greatly needed for early detection of nervous system dysfunction in people working with neurotoxic substances. Previous studies showed long-term solvent exposure may cause visual perception deficits; thus, the effect of long-term occupational solvent exposure and chronic encephalopathy on performance in 3 vision tests novel in this context were studied. In both visual search tasks, patients were statistically highly significantly slower than age-matched control observers. In the contrast sensitivity test, the difference between patients and control group was small relative to normal variability, although still statistically significant. Results suggested visual search tests can be useful to evaluate and characterize the effect of long-term solvent exposure on visual perception. Since the patient letter contrast sensitivity was only moderately deteriorated, it seemed the observed defect of visual search cannot be explained by deteriorated letter identification alone, although it can be a contributory factor. Rather, results suggested the speed by which visual information is transmitted and/or processed in the central visual system became considerably slower.
Authors: Naesaenen, Risto; Kaukiainen, Ari; Hero, Ville; Paaseelysaho, Juha; Mueller, Kiti; Hari, Riitta; Akila, Ritva; Sainio, Markku
Full source: Environmental Toxicology and Pharmacology 2005, 19(3), 497-504 (Eng)