

Featured Research Studies

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Genetic evaluation of the serotonergic system in chronic fatigue syndrome.

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Chronic fatigue syndrome (CFS) is a debilitating disorder of unknown etiology with no known lesions, diagnostic markers or therapeutic intervention. The pathophysiology of CFS remains elusive, although abnormalities in the central nervous system (CNS) have been implicated, particularly hyperactivity of the serotonergic (5-hydroxytryptamine; 5-HT) system and hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Since alterations in 5-HT signaling can lead to physiologic and behavioral changes, a genetic evaluation of the 5-HT system was undertaken to identify serotonergic markers associated with CFS and potential mechanisms for CNS abnormality. A total of 77 polymorphisms in genes related to serotonin synthesis (TPH2), signaling (HTR1A, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR4, HTR5A, HTR6, and HTR7), transport (SLC6A4), and catabolism (MAOA) were examined in 137 clinically evaluated subjects (40 CFS, 55 with insufficient fatigue, and 42 non-fatigued, NF, controls) derived from a population-based CFS surveillance study in Wichita, Kansas. Of the polymorphisms examined, three markers (-1438G/A, C102T, and rs1923884) all located in the 5-HT receptor subtype HTR2A were associated with CFS when compared to NF controls. Additionally, consistent associations were observed between HTR2A variants and quantitative measures of disability and fatigue in all subjects. The most compelling of these associations was with the A allele of -1438G/A (rs6311) which is suggested to have increased promoter activity in functional studies. Further, in silico analysis revealed that the -1438 A allele creates a consensus binding site for Th1/E47, a transcription factor implicated in the development of the nervous system. Electrophoretic mobility shift assay supports allele-specific binding of E47 to the A allele but not the G allele at this locus. These data indicate that sequence variation in HTR2A, potentially resulting in its enhanced activity, may be involved in the pathophysiology of CFS.

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Weight gain associated with chronic exposure to chlorpyrifos in rats.

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OBJECTIVE: This work exposed rats to low levels of the organophosphate insecticide chlorpyrifos and monitored for toxic effects, including weight gain. **METHODS:** Rats received either a subcutaneous injection of chlorpyrifos, 5 mg/kg/day, or an equal volume of vehicle daily for 4 months. Subjects were observed for 30 minutes after injection for signs of acute toxicity. Body weights were recorded at baseline, 2 months, 3 months, and 4 months. At the end of the experiment, the weights of hearts, medial lobe of the livers, peri-nephric fat pads, and gastrocnemius muscles were recorded. Effects of chlorpyrifos on adipocyte differentiation in culture were studied. Results were compared using RMANOVA. **RESULTS:** No signs of acute cholinergic toxicity were observed after injections in any subject. Rats in the 5 mg/kg group were significantly heavier than those in the control group by 2 months (335.7 +/- 16.7 g vs. 318.6 +/- 15.8 g; $p = 0.034$). This difference increased at 3 months (350.1 +/- 16.4 g vs. 322.3 +/- 21.3 g $p = 0.006$) and 4 months (374.4 +/- 22.2 g vs. 340.2 +/- 25.2 g $p = 0.006$). At 4 months, the weights of the perinephric fat pads were significantly increased in the chlorpyrifos group relative to controls (2.867 + 0.516 vs. 1.130 + 0.171, $p = 0.0039$). The two groups showed no weight differences between hearts, livers, and gastrocnemius muscles. Chlorpyrifos did not affect adipocyte differentiation in tissue culture. **CONCLUSIONS:** Chronic exposure to chlorpyrifos at 5 mg/kg/day caused an increase in rat body weight when compared to controls. This increase was in adipose tissue. Chlorpyrifos did not induce differentiation of adipocytes in culture.

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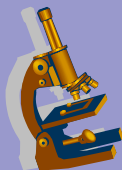
Development and validation of a chemical hydrolysis method for dextromethorphan and dextrophan determination in urine samples: Application to the assessment of CYP2D6 activity in fibromyalgia patients.

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Dextromethorphan (DEM) is a widely used probe drug for human cytochrome P450 2D6 isozyme activity assessment by measuring the ratio between DEM and its N-demethylated metabolite dextrophan (DOR). DOR is excreted in urine mainly conjugated to glucuronic acid. Prior to quantification, DOR must be deconjugated to avoid variability caused by the polymorphic glucuronosyltransferase enzyme. A chemical hydrolysis method was optimized using a chemometric approach. Three factors (acid concentration, hydrolysis time and temperature) were selected and simultaneously varied to study their effect on conjugated DOR hydrolysis. Hydrolysis conditions that maximize DOR release without significant degradation of both DEM and DOR were chosen and results were compared to those obtained by enzymatic method using beta-glucuronidase. An HPLC method with fluorescence detection was developed for the simultaneous quantitation of DEM, DOR and levallorphan, used as an internal standard. Separation was performed on a phenyl analytical column (150mmx4.6mm i.d., 5µm) with a mobile phase consisting of 18% acetonitrile and 50mM phosphoric acid (pH 3). The overall analytical procedure was validated and showed good performances in terms of selectivity, linearity, sensitivity, precision and accuracy. Finally, this assay was used to determine DEM/DOR molar ratios in fibromyalgia patients for the purpose of determining phenotype status for the CYP2D6.

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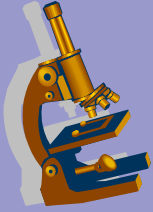
Urinary phthalate metabolites and semen quality: a review of a potential biomarker of susceptibility.

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Phthalates are a class of chemicals with widespread general population exposure. Some phthalates are reproductive and developmental toxicants in laboratory animals. Advances in the field of phthalate research in humans are dependent on the development and implementation of biomarkers to assess exposure and outcome, as well as potential markers that may be indicative of increased susceptibility. Recently, we incorporated a novel biomarker of potential 'susceptibility' into our study on the relationship of phthalates with semen quality and sperm DNA damage among men recruited from an infertility clinic. We measured urinary concentrations of three di(2-ethylhexyl) phthalate (DEHP) metabolites, mono(2-ethylhexyl) phthalate (MEHP) and two oxidative metabolites, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP). We calculated the percent of DEHP excreted as the hydrolytic monoester (i.e., MEHP). We referred to this as %MEHP and considered it a phenotypic marker of the proportion of DEHP excreted in the urine as MEHP. In our sperm DNA study, we found novel results for the DEHP metabolites. Although MEHP was positively correlated with the oxidative metabolites, the association of sperm DNA damage with MEHP, as compared to MEHHP and MEOHP, were in opposite directions. We hypothesized that MEHP is the bioactive toxicant and further metabolism to MEHHP/MEOHP may lower internal burden of MEHP and thus be protective from sperm DNA damage. An alternative explanation may include that the relative percentage of DEHP excreted as MEHP was a surrogate for the function of phase I enzymes. Men with high %MEHP may have higher levels of sperm DNA damage because of poor metabolism (detoxification) of other genotoxic chemicals. Our hypothesis that %MEHP may represent a phenotypic marker of metabolism is novel but requires further exploration to confirm.

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Nasal hyperreactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness.
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Self-reported non-allergic nasal symptom triggers in non-allergic ('vasomotor') rhinitis overlap with commonly identified environmental exposures in non-specific building-related illness. These include extremes of temperature and humidity, cleaning products, fragrances, and tobacco smoke. Some individuals with allergic rhinitis also report non-allergic triggers. We wished to explore the phenotypic overlap between allergic and non-allergic rhinitis by ascertaining self-reported non-allergic nasal symptom triggers among allergic rhinitics. Sixty subjects without work-related respiratory exposures or symptoms, aged 19-68 years, stratified by age, gender and (skin test-proven) allergic rhinitis status, were queried with regard to self-reported non-allergic nasal symptom triggers (aggregate score 0-8). In this sample, the number of self-reported non-allergic triggers was bimodal, with peaks at 1 and 5. Forty-two percent of seasonal allergic rhinitic subjects reported more than three non-allergic triggers, compared with only 3% of non-allergic non-rhinitics ($P < 0.01$). Subjects over 35 years were more likely to report one or more non-allergic triggers, particularly tobacco smoke ($P < 0.05$). Allergic rhinitics reported more non-allergic symptom triggers than did non-allergic, non-rhinitics. As indexed by self-reported reactivity to non-specific physical and chemical triggers, both non-allergic rhinitics and a subset of allergic rhinitics may constitute susceptible populations for non-specific building-related illness. PRACTICAL IMPLICATIONS: Judging by self-report, a substantial subset of individuals with allergic rhinitis--along with all individuals with nonallergic rhinitis (by definition)--are hyperreactive to non-allergic triggers. There is overlap between these triggers (elicited in the process of obtaining a clinical diagnosis) and environmental characteristics associated with "problem buildings." Since individuals with self-identified rhinitis report an excess of symptoms in most epidemiologic studies of problem buildings (even in the absence of unusual aeroallergen levels), rhinitics may be acting as a "sentinel" subgroup when indoor air quality is suboptimal. Together, non-allergic rhinitics plus allergic rhinitics with prominent non-allergic triggers, are thought to constitute approximately one-sixth of the US population

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