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Introduction: Traumatic brain injury (TBI) can disrupt the hypothalamo-pituitary axis, causing central neuroendocrine dysfunction and hormone abnormalities (HPAD). As one-third of children can develop post-traumatic HPAD, a longitudinal and thorough follow up may be required to exclude the transient or late-onset HPAD.
Objective: To implement a protocol for standardized evaluation of children with TBI for the diagnosis of HPAD and to effectively establish a regular inpatient endocrine consultation and outpatient longitudinal follow up. **Method:** The study was divided into pre-QI (baseline phase) and QI phase (post-intervention phase). During the pre-QI phase, retrospective data were collected on children admitted with TBI at our institution for 1 year. The prevalence of HPAD and the percentage of children longitudinally followed in endocrine clinic were estimated. A consensus-based guidance protocol, detailing clinical and hormonal assay-based evaluation at presentation and during the follow up were formulated and implemented. Prospective data collection will be performed to estimate outcome measures (prevalence of HPAD, rate of initial endocrine consultation and endocrine outpatient follow up) and process measure (protocol adherence rate). **Result:** During the baseline phase (pre-QI), a total of 27 children, aged ≤19 years were admitted in the year for TBI management. The median (IQR) age at TBI diagnosis was 9 (3, 15) years. Motor vehicle accident was the predominant cause, accounting for 60%. In 85% of patients, the TBI was classified as severe based on GCS. Overall, only 8 children (30%) underwent limited (non-consultation based) endocrine evaluation (7 for central DI and 1 for central hypothyroidism) and 1 patient had complete evaluation (endocrinologist consulted). During the baseline period, the prevalence rate of transient central DI was diagnosed in 1 patient (4%). Implementation of protocol and post-intervention data collection are pending. **Conclusion:** The lower prevalence rate of HPAD in the current cohort of TBI patients may be due to under evaluation for endocrine dysfunction. QI initiative incorporating standardized evaluation using guiadance protocol will improve identification follow up rates of patients with endocrine dysfunction following TBI.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

The Association of the Polychlorinated Biphenyl Class of Endocrine Disruptors With Polycystic Ovary Syndrome and Thyroid Dysfunction

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Introduction:. Polychlorinated biphenyls (PCBs) are a class of endocrine disruptors with a long half-life in the body that are associated with irregular menses, growth and development delay, increased cancer risk, thyroid disorders and an increased risk of diabetes. Higher levels of PCBs have been related to polycystic ovary syndrome (PCOS). PCB toxicity depends on their structure, with coplanar PCBs being most toxic (akin to dioxins); therefore, PCB subtypes were determined to see if they differed in women with PCOS compared to normal controls. **Methods:**. PCB levels were compared in Caucasian women with (n=29) and without (n=30) PCOS and related to metabolic features. PCBs were fractionated then analysed by high-resolution gas chromatography-unit resolution mass spectrometry. **Results:.** The control and PCOS groups were age and BMI matched (p=ns); insulin resistance was not different (HOMA 1.7±1.0 v 2±1.6, p=ns) but free androgen index was increased in PCOS ($p<0.004$). PCB-118, 138, 153 and 180 were found in all subjects, whilst fewer subjects showed PCB-28(15/59), PCB-52(4/59) or PCB-101(26/59). There was no difference for PCB-188,138,153 and 180 between controls and PCOS, but all correlated with increasing age ($p<0.01$) and decreasing estimated glomerular filtration rate ($p<0.05$); no correlations with BMI, HOMA, testosterone, TSH or T3 were found; however, PCB-118 (the only coplanar PCB detected) associated with an increased T4/T3 ratio ($p<0.01$). **Conclusion**. Despite PCBs being banned over a decade ago, PCBs were detected, but did not differ between age and BMI matched women with and without PCOS. Thyroid dysfunction may be only associated with toxic coplanar PCBs, such as PCB-118 that was associated with a higher T4/T3 ratio.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

The Effect of the GH/IGF-1 Axis During Trypanosoma Cruzi Infection

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Trypanosoma cruzi is the parasite responsible for Chagas disease (CD), that affects 6-8 million people worldwide. CD treatment is limited to two drugs (benznidazole and nifurtimox). Treatment is mostly effective during the acute phase of the disease (initial two months post-infection), while their efficacy during the chronic phase is controversial. In the absence of treatment, 30% of infected individuals suffer irreversible chronic cardiac and digestive damages, which lead to inability and, in some instances, death. Patients with Laron Syndrome (LS, a form of congenital GH insensitivity) are short in stature with low levels of IGF-1, elevated levels of GH and, surprisingly, are resistant to cancer and diabetes. A cohort of LS patients living in southern Ecuador, where CD is endemic, has been studied by Dr. Jaime Guevara for over 25 years (1). Few, if any, cases of CD have been reported among these patients (Dr.

Guevara, personal communications). *T. cruzi* infection has been shown to directly modulate pituitary hormones such as GH, PRL and glucocorticoids (stress related hormones), leading to immunosuppression and thymic atrophy by depletion of $CD4^+$ $CD8^+$ cells. Previously, rats infected with *T. cruzi* and treated with GH showed reduced parasitism and less tissue damage compared to controls (2). The purpose of this research is to investigate the *in vitro* effect of GH during *T. cruzi* infection, simulating conditions of GH insensitivity. First, we separately treated *T. cruzi* and the host cells [human cervical cancer cell line (HeLa) and male mouse fibroblast (L-cells)] with relatively low or high levels of GH, IGF-1, PRL, and EGF. Next, we treated the parasite and host cells simultaneously with these hormones. When the parasites were treated alone, *T. cruzi* responded to exogenous GH (5ng/ml-50ng/ml) by significantly increasing the percentage of amastigotes (less infective form of the parasite). Also, when GH (50ng/ml) were administered to the host cells, *T. cruzi* infectivity was significantly reduced by 12% (percentage of infection) compared to 20% from untreated conditions. Similarly, both parasite and host cells treated with GH significantly reduced *T. cruzi* infectivity (10%) compared to untreated conditions (18%). We further treated both cell lines with a combination of GH/IGF-1. Conditions used were as follows: control (no-treatment), moderate levels (5ng/ml GH+150 ng/ml IGF-1), relatively high levels (50ng/ml GH+600ng/ml IGF-1), or levels that would simulate those found in patients with LS(50ng/ml GH+20 ng/ml IGF-1). Of these, the LS concentrations significantly reduced infection in both cell lines (11%) compared to control (16%). Together these results indicate that GH can influence *T. cruzi* infectivity and that GH, not IGF-1, is mediating the decreased infectivity. Finally, the results suggest that high concentrations of GH, as seen in LS patients, could be protective during *T. cruzi* infection.
1)Guevara-Aguirre et al., 2011 2) Frare et al., 2010

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

The Effects of Naphthenic Acids on Tryptophan Metabolism and Peripheral Serotonin Signalling

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Introduction: Serotonin produced in the periphery has been shown to affect glucose and lipid homeostasis. The availability of the amino acid tryptophan, the precursor of serotonin, affects serotonin availability. In addition, the metabolism of tryptophan via the kynurenine pathway produces physiologically active metabolites which have been shown to be altered under conditions of increased adiposity and dysglycemia. There is now evidence demonstrating some environmental xenobiotics, known to affect glucose and lipid homeostasis, can also alter serotonin production and key components of the kynurenine pathway. Recent evidence suggests that exposure to compounds present in petroleum and wastewaters from oil and gas extraction sites can impact endocrine signaling and result in aberrant lipid accumulation and altered glycemic control. However, whether any of these changes can be causally ascribed to altered serotonin synthesis/signaling or tryptophan metabolism remains unknown. The goal of this study was to determine the effects of exposure to naphthenic acid (NA), a key toxicant found in wastewater from bitumen (thick crude oil present in oil sands deposits) extraction on the enzymes involved in tryptophan metabolism and serotonin production.
Methods: McA-RH7777 rat hepatoma cells, were exposed to a technical NA mixture for 48 hours at concentrations within the reported range of NA found in wastewaters from oil extraction. We assessed mRNA expression for key rate-limiting enzymes involved in tryptophan metabolism that lead to either serotonin [*Tph1*] and/or kynurenine [*Ido2* and *Tdo2*] production, as well as downstream enzymes in the kynurenine pathway [*Afmid*, *Kyat1*, *Aadat*, *Kyat3*, *Kmo*, *Haao*, *Acmsd*, *Qprt*]. We also examined the effects of NA on prostaglandin synthesis [*Ptgs1*, *Ptgs2, Ptges*] and signalling [*Ptger2*, *Ptger4*] as prostaglandins have been shown to be induced by serotonin and are linked to hepatic fat accumulation.
Results: NA treatment significantly increased *Tph1* and *Ido2* expression; this occurred in association with a significant increase in the expression of the inducible prostaglandin synthase *Ptgs2* (COX-2), prostaglandin E synthase *Ptges,* and prostaglandin receptors *Ptger2* and *Ptger4*. *Acmsd* was the only downstream enzyme in the kynurenine pathway that was significantly altered by NA treatment.
Conclusion: These results provide proof-of-concept that compounds associated with oil sands extraction have the potential to perturb key components of serotonin synthesis (*Tph1*) and tryptophan metabolism (*Ido2*, *Acmsd*). Furthermore, we found that the increase in *Tph1* expression paralleled expression of *Ptgs2*. As increased prostaglandin production has been reported in association with nonalcoholic steatohepatitis, these data provide a potential mechanism by which exposure to NA and other petroleum-based compounds may increase the risk of metabolic disease.

Endocrine Disruption

ENDOCRINE DISRUPTING COMPOUNDS: MECHANISMS OF ACTION AND CLINICAL IMPLICATIONS

The Effects of Tert-butyl Hydroquinone (TBHQ) on Estrogen Receptor Alpha (ERα) and Tumor Suppressor Gene p53 in Breast Cancer Cells

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Tert-butyl hydroquinone (TBHQ) is an aromatic compound that is commonly used as a preservative in processed food to prevent rancidity and lengthen shelf life. TBHQ is known to act as an antioxidant by protecting cells from radical oxygen