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