transporters in the placenta, including the breast cancer resistance protein (human BCRP/mouse Bcrp), also limit fetal exposure by returning Cd back to the maternal circulation. We have previously demonstrated that placental BCRP expression confers a 7-fold resistance against Cd toxicity *in vitro*. In this study, we sought to determine whether the absence of Bcrp in the placenta alters the fetoplacental disposition and toxicity of Cd in mice. Pregnant female C57BL/6Crl (WT) and Bcrp-null mice (n=9-10/group) were administered a single dose of saline (5 ml/kg ip) or $CdCl_2$ (5 mg/kg ip) on gestational day (GD) 9. On GD 17, fetuses and placentas were collected. As expected, no Bcrp expression was detected in Bcrp-null offspring. Compared to vehicle-treated WT dams, there were a number of basal differences in Bcrp-null dams including 1) lower weight gain across gestation, 2) larger lumens (45%) of fetal-derived vessels in the placental labyrinth 3) elevated mRNA expression (3-fold) of the divalent metal micronutrient transporters, *Zip14, Znt1,* and *Dmt1* and 4) enhanced expression of alternate efflux transporter Mdr1a (9-fold) and Mdr1b (14-fold) mRNAs. Collectively, these adaptive changes may be responsible for the similar basal sizes of WT and Bcrp-null offspring. Following Cd treatment, fetal length and placental area were reduced in both genotypes compared to respective controls. Moreover, Cd-treated Bcrp-null fetuses had a 12% shorter crown-to-rump length than Cd-treated WT offspring. Shorter fetuses corresponded with preferentially higher Cd accumulation (58%) in Bcrp-null placentas despite the higher Mdr1a/1b expression. To delineate mechanisms underlying the reduced growth in Bcrp-null fetuses after Cd treatment, changes in placental vasculature and nutrient transport were examined. Notably, placentas from Bcrp-null offspring had reduced expression of metal transporters (34% decrease in Zip14 mRNA and 58% decrease in Dmt1 protein) following Cd treatment. The absence of Bcrp alters development of the placenta and results in increased accumulation of Cd and impaired fetal growth potentially due to reduced uptake and transfer of essential nutrients. *Supported by F31ES032319, R01ES029275, T32ES007148, and P30ES005022.*

3555 Chronic Inhalation of Titanium Dioxide Nanoparticles Disrupts Placental Glucose Transporter Expression

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Maternal inhalation of particulate during pregnancy has been linked to perinatal death and various adverse health conditions in adulthood, including diabetes and cardiovascular disease. Of these xenobiotic exposures, titanium dioxide (TiO_2) is a non-reactive particle found in consumer and personal care products. Previous lab data demonstrated a significant correlation between maternal exposure and fetal growth restriction. The etiology of this developmental concern may have maternal, fetal, and placental origins. Of interest is compromised placental function leading to impaired placental transport of nutrients to the fetus. Glucose transport is a critical component in healthy fetal development; therefore, we chose to examine the integrity of glucose transport mechanisms. We hypothesized maternal inhalation of TiO_2 particles would lead to a reduction in glucose transporter expression, resulting in less glucose transport to the fetus to support proper growth. Pregnant Sprague Dawley rats were exposed to TiO_2 powder (Aeroxide TiO_2, Parsippany, NJ) aerosols [11.04 ± 1.09 mg/m^3; geo. mean particle size 162.06 ± 5.30 nm (SMPS, TSI)] via a whole-body inhalation chamber (HPGA, IESTechno) from gestational day (GD) 4-19 for 4-5 hours a day. On GD20, maternal plasma was collected, and four placentas were taken from each dam at varying intrauterine positions. Placentas were sliced in half along the sagittal plane and prepped for immunohistochemistry. GLUT1, GLUT3, and GLUT4 antibodies were used to visualize and quantify glucose transporter expression in the labyrinth zone. We observed a significant increase in the staining intensity of GLUT4 in placentas of exposed animals when compared to controls (91.40 ± 4.98 vs. 74.66 ± 1.49; p=0.03). When separated by sex, it became evident male placentas drove this significance (70.85 ± 6.94 in control males vs. 94.27 ± 3.94 in exposed males; p=0.01) as opposed to females (78.47 ± 8.26 in control females vs. 88.53 ± 7.90 in exposed females; p=0.36). Since GLUT4 is known to be insulin-regulated, maternal insulin was measured in plasma samples using an ELISA, revealing an insignificant increase of insulin in exposed dams. GLUT1 showed a trending decrease in staining intensity (p=0.07) and when separated by sex, female placentas showed a significant decrease in staining intensity after exposure compared to controls (72.38 ± 0.87 vs. 81.28 ± 1.76, respectively, p=0.002). There were no significant changes in GLUT3 staining. Collectively, these data identify sex dependent alterations in glucose transport expression in the placenta. Glucose is an important energy source for both the placenta and the fetus; therefore, this warrants a closer examination of placental handling and metabolism of glucose, which is currently under investigation. These effects may reveal impairments in placental health after TiO_2 exposure from personal care products. *Supported by: NIH-R01-ES031285; T32-ES007148; P30-ES005022; R25-GM055145.*

3556 Maternal Nano-itanium Dioxide Inhalation Exposure during Gestation Affects Placental Anatomy in a Sex-Dependent Way

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Maternal nano-titanium dioxide (nano-TiO2) inhalation during pregnancy is associated with poor gestational outcomes including decreased fetal weight, endocrine disruption, decreased placental weight, and altered vasoreactivity. The placenta consists of two distinct zones; the junctional zone (JZ), which is important for endocrine function; and labyrinth zone (LZ), important for maternofetal nutrient and waste transfer. Therefore, the aim of this study was to determine if the effects of maternal nano-TiO2 inhalation during gestation on fetal weights, JZ and LZ weights, and JZ and LZ percent area are dependent upon the sex of the fetus. Pregnant Sprague-Dawley rats were exposed to either nano-TiO2 aerosols or HEPA filtered air and sacrificed on gestational day (GD) 20. Male and female pups were collected from each dam and weighed, as well as their corresponding placentas, where dry and wet weights of the JZ and LZ were measured. Additionally, placenta slices (10 µm) were taken and hematoxylin and eosin staining were run to determine percent area of the JZ and LZ. No significant differences were seen in male pups in any endpoint between nano-TiO2 or air exposure. Wet female fetal weight was decreased in the nano-TiO2 exposed group (2.65 ± 0.03 g) as compared to the sham-control group (2.74 ± 0.03 g; $p < 0.05$). Dry fetal weight displayed similar results, showing a decreased weight in nano-TiO2 exposed (0.33 ± 0.01 g), compared to sham-control (0.34 ± 0.01 g; $p < 0.05$). Wet JZ weight was decreased in nano-TiO2 exposed (0.18 ± 0.01 g) versus sham-control (0.23 ± 0.01 g). Similarly, dry JZ weight was increased in sham-control (0.046 ± 0.003) and decreased in nano-TiO2 exposed (0.028 ± 0.001 g). There was no difference in the dry LZ weight between sham-control and the nano-TiO2 group, however, the wet LZ was slightly smaller in the nano-TiO2 group (0.3033 ± 0.006) than in the sham-control group (0.3128 ± 0.013). Percent JZ area was significantly decreased in the nano-TiO2 exposed group (24.37 ± 1.30 %) compared to the sham-control (30.39 ± 1.54 %; $p < 0.05$). Conversely, the percent LZ area was significantly increased in the nano-TiO2 exposed group (75.63 ± 1.30 %) versus the sham-control group (69.61 ± 1.54 %; $p < 0.05$). These studies represent evidence that maternal inhalation of nano-TiO2 during gestation causes anatomical changes within the placenta, creating a smaller JZ in female pups and potentially leading to decreased hormonal efficiency. *This work was supported by the following sources: WV-CTSI U54 GM104942-05, K01 10029010 (ECB), T32 AG 52375 (JAG), P20 GM103434 (WV-INBRE).*

3557 The Xanthine Oxidoreductase Inhibitor Febuxostat Protects against Nanomaterial Inhalation–Induced Microvascular and Reproductive Dysfunction during Gestation

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Maternal inhalation exposure to nano-TiO_2 during gestation impacts litter size, pup and placental mass, and uterine microvascular reactivity. In addition, we have recently shown that maternal inhalation of nano-TiO_2 during gestation results in redox imbalance in dams during late gestation. However, the mechanism linking these dysfunctions with exposure has yet to be explored. Therefore, we hypothesized that elevated xanthine oxidoreductase (XOR), a critical source of oxidants in numerous inflammatory processes, is at least partially responsible for the increased oxidant production observed. The objective of this study was to assess if treatment with a XOR inhibitor, febuxostat (Uloric), rescues the poor microvascular and reproductive outcomes induced by gestational nano-TiO_2 exposure. Female Sprague Dawley rats, 6-8 weeks of age, received febuxostat treated water (50 mg/L) beginning one week prior to being mated in-house and throughout gestation until sacrifice on gestational day (GD) 20. Once pregnant, dams were randomly assigned to either sham-control (N = 4) or nano-TiO_2 (N = 4) groups. Dams were exposed (nano-TiO_2 concentration = 12 mg/m^3; HEPA-filtered air 25 ml/min) for 6 hrs/d for 6 d between GD 10-19 before sacrifice on GD 20. Dam and litter characteristics as well as placental and fetal weights were recorded at the time of sacrifice. No significant differences were observed between sham-control and nano-TiO_2 groups for litter size (9.6±3.3 versus 12.6±2.2), fetal (3.8±0.1 g versus 4.0±0.9 g) or placental mass (0.72±0.03 g versus 0.65±0.02 g). Additionally, uterine arteries were isolated, and reactivity was assessed *ex vivo*. Uterine arteries from exposed females treated with febuxostat showed similar vasoconstriction to kisspeptin (97.6%±1.95) as control females given febuxostat (99.8%±0.61), and decreased kisspeptin induced vasoconstriction from what has been previously observed in directly exposed nano-TiO_2 dams (75.1%±14.2). Additionally, there was no difference in dam liver mass (11.5%±0.80 g control versus 13.9%±0.60 g nano-TiO_2), which we have previously shown to be increased due to nano-TiO_2 exposure. Taken together, these observations indicate that reproductive, liver, and microvascular functions are protected, at least in part, from nano-TiO_2 inhalation exposure induced dysfunction in pregnant dams by XOR inhibition. *Support: OH012320 (EB), ES015022 (TN), ES032920 (JG).*

62nd Annual Meeting & ToxExpo
Nashville, TN • March 19–23, 2023

The Toxicologist

Supplement to *Toxicological Sciences*

SOT | Society of Toxicology

Toxicological Sciences

The Official Journal of the Society of Toxicology

OXFORD UNIVERSITY PRESS

ISSN 1096-6080 Volume 192, Issue S1 March 2023
www.academic.oup.com/toxsci

Publication Date: March 14, 2023