Sexually Dimorphic Thyroid Gene Expression Can Lead to Sex-Specific Responses to Thyroid-Disrupting Compounds

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Sexually Dimorphic Thyroid Gene Expression Can Lead to Sex-Specific Responses to Thyroid-Disrupting Compounds

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The thyroid hormone (TH) system is central to brain development and is susceptible to perturbation by environmental chemicals. Testing of chemicals for TH disruption is often done in animals, but to allow for the use of alternative test methods, mechanism of effects must be better described. Ex vivo thyroid culture is a tractable model, as it can be used both as an intermediate model system and for characterizing mechanisms-of-action. In this project, we aim to characterize sex differences in thyroid development and developmental windows of TH system vulnerability to chemical exposure to facilitate better design and interpretation of ex vivo thyroid culture. Initial studies using explanted rat fetal thyroids exposed for 72 and 120 h to 100 µM propylthiouracil (PTU) revealed that i) key genes are dysregulated by PTU exposure and ii) the thyroids have sex-specific transcriptional profiles that give rise to sex-specific responses to chemical insult. Genes, including Tshr and Nkx2-1, displayed sexually dimorphic expression patterns after 72 h culture, a sex difference that disappeared after 120 h culture. After exposure to PTU, a thyroperoxidase (TPO) inhibitor, we observed compensations in both males and females. In males, these compensatory mechanisms were identified as upregulated Nis expression in response to PTU exposure, as well as a trend for upregulated Tpo and Tg expression with no effects on Tshr. In females, there was only a trend towards upregulated Nis expression, no effect on Tpo and Tg, and a downregulation of Tshr. These findings suggest sexually dimorphic effects in response to chemical exposure. These sex differences have implications for interpretation of thyroid disruption in animal studies and for further development of test methods for TH disruption. SOT 59th Annual Meeting and ToxExpo 2