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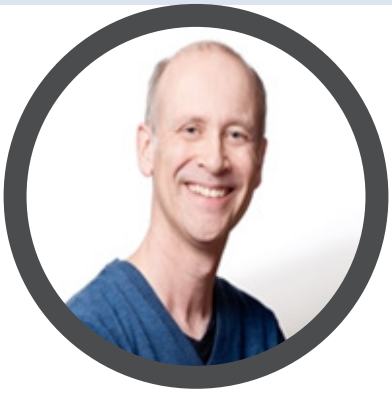
DEVELOPMENT AND APPLICATION OF PHYSIOLOGICALLY RELEVANT IN VITRO MODELS OF HUMAN STEROIDOGENESIS IN TOXICOLOGY: THE ENDOCRINE DISRUPTING POTENTIAL OF NEONICOTINOID PESTICIDES IN HUMANS



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Humans are exposed to thousands of environmental chemicals with poorly understood toxicological properties. In vivo toxicity testing is time-consuming, costly and ethically questionable because of the large numbers of laboratory animal required. Although current in vitro models have considerably improved our understanding of chemical mechanisms of toxicity, these systems mostly determine single endpoints in single cell types, which poorly reflect the intact organism. The goal of my laboratory is to better reproduce in vivo interactions by developing co-culture models that incorporate physiologically relevant intercellular communications. Our focus is on steroidogenesis, an important but poorly studied target for endocrine disrupting chemicals. In humans, sex steroid hormones are essential for healthy reproduction and pregnancy, but are also involved in diseases such as hormone-dependent breast cancer. Aromatase (*CYP19*) converts androgens to estrogens and, unlike in non-primates (e.g. rodents), where it is expressed only in gonads and brain, human aromatase is expressed in numerous tissues including mammary gland (where it is overexpressed in hormone-dependent breast cancer) and placenta using tissue-specific promoters. As rodent models are inadequate, we developed several physiologically relevant human in vitro models to evaluate the effects of neonicotinoid insecticides, a poorly studied class of emerging pesticides, on sex hormone biosynthesis. Cellular co-culture models of the feto-placental unit and human breast tumor microenvironment were used to determine effects of neonicotinoids on steroid production and promoter-specific regulation of *CYP19*. Neonicotinoids increased *CYP19* gene expression promoter-specifically in our human co-culture models. In the feto-placental co-culture model, neonicotinoids increased estradiol and estrone, but strongly inhibited estriol production. In our breast cancer model, neonicotinoids induced a promoter-switch in *CYP19* expression, with silencing of normal mammary promoter 1.4 and activation of pro-cancerous promoters PII, 1.3 and 1.7, resulting in aromatase overexpression, similar to that observed clinically in patients. These are the first studies to document in vitro, disruptive effects of neonicotinoids on human steroidogenesis in physiologically relevant multi-cell systems.

Biography

Thomas Sanderson has obtained his PhD from the University of British Columbia, Vancouver, Canada and did Postdoctoral studies at Michigan State University, USA. He is an Associate Professor at the INRS-Institut Armand-Frappier, Laval (Québec), Canada and has published more than 70 papers in reputed journals. His toxicology laboratory is focused on studying interactions of chemicals with steroidogenic enzymes in humans and wildlife and is currently funded by the Natural Sciences and Engineering Council (NSERC) of Canada and the Alternatives Research and Development Foundation (USA). He is Editorial Board Member of *Toxicological Sciences and Peer J.*

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