Universität Basel

Research Project

Xenobiotics disrupting the corticosteroid – androgen balance

Third-party funded project

Project title Xenobiotics disrupting the corticosteroid – androgen balance
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Corticosteroids have key roles in regulating essential physiological processes. Impairment of corticosteroid homeostasis has been associated with metabolic and cardiovascular disease, cancer, immune disorders and behavioural diseases. Importantly, corticosteroid and androgen signalling pathways influence each other and a tight regulation is essential to maintain body homeostasis. For example, glucocorticoids exert catabolic effects, and they inhibit proliferation and promote differentiation in many cell types, controlling essential developmental processes. In contrast, androgens act anabolic and promote the proliferation of several cell types, including cancer cells. Further, glucocorticoids inhibit testicular testosterone synthesis and sperm production, whilst androgens stimulate it. Moreover, glucocorticoids promote visceral obesity and fatty liver disease, whereas androgens exert protective effects (although regarding fatty liver disease sex-specific differences need to be taken into account).

Increasing evidence indicates that, besides genetic predisposition, the exposure to xenobiotics can contribute to the development and progression of major diseases. However, despite the key role of corticosteroids and the corticosteroid – androgen balance, the impact of xenobiotics disrupting their function represents a neglected topic and research on endocrine disrupting chemicals (EDC) focused largely on estrogen receptors and reproductive toxicity (1, 2).

In the proposed project, we investigate xenobiotics (environmental pollutants, industrial and occupationally relevant chemicals, body care products, food additives, supplements, recreational drugs, pharmaceuticals) that might disrupt the corticosteroid – androgen balance and how they do that. In **WP1** we investigate xenobiotics-induced **disturbances of corticosteroid – androgen balance in human and animals** by **assessing steroid concentrations** and by attempting to **define steroid metabolites and ratios** thereof that serve **as indicators of disturbances**. Such markers of disturbed corticosteroid – androgen balance will facilitate the investigation of potential EDCs disturbing this balance. It should ultimately allow testing for correlation between a given compound, a steroid marker and a physiologic, respectively a disease read-out. In **WP2**, we aim at investigating **mechanisms of action of EDCs disturbing corticosteroid – androgen balance** in **cell-based models**, focusing on glucocorticoid- and androgen **receptor resistance** and on mechanisms of **altered expression of** glucocorticoid and androgen metabolizing **enzymes**. Finally, in **WP3** we aim to extend our previously established expertise and tools to **identify hazardous chemicals** and to study **chemical-protein interactions** (3-9), providing novel information for molecular initiating events (MIE). These studies mainly focus on two topics: 1) xenobiotics interfering with corticosteroid synthesis/metabolism and causing **mineralocorticoid-dependent hypertension and cardiovascular disease**; and 2) xenobiotics disturbing glucocorticoid – androgen balance

in **hepatocytes** and adipocytes and contributing to **non-alcoholic fatty liver disease (NAFLD)** and visceral obesity. Xenobiotics identified in the in silico/in vitro testing will be further investigated using cell-based models in WP2 and if appropriate, in animals and in human in WP1.

Keywords endocrine disrupting chemical, xenobiotic, androgen, glucocorticoid, corticosteroid, hazardous chemical, disease
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Follow-up project of 3851234 Chemicals Disrupting Adrenal Steroidogenesis and/or Peripheral Steroid Action

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