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2022

This article was originally published at:
https://doi.org/10.1016/j.envres.2021.111906

Environmental Research 203 (2022) 111906

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Disruption by stealth - Interference of endocrine disrupting chemicals on hormonal crosstalk with thyroid axis function in humans and other animals

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ARTICLE INFO

Keywords:
Endocrine disruptor
Thyroid hormone
Crosstalk
Reproductive hormones
Stress

ABSTRACT

Thyroid hormones (THs) are important regulators of growth, development, and homeostasis of all vertebrates. There are many environmental contaminants that are known to disrupt TH action, yet their mechanisms are only partially understood. While the effects of Endocrine Disrupting Chemicals (EDCs) are mostly studied as "hormone system silos", the present critical review highlights the complexity of EDCs interfering with TH function through their interactions with other hormonal axes involved in reproduction, stress, and energy metabolism. The impact of EDCs on components that are shared between hormone signaling pathways or intersect between pathways can thus extend beyond the molecular ramifications to cellular, physiological, behavioral, and whole-body consequences for exposed organisms. The comparatively more extensive studies conducted in mammalian models provides encouraging support for expanded investigation and highlight the paucity of data generated in other non-mammalian vertebrate classes. As greater genomics-based resources become available across vertebrate classes, better identification and delineation of EDC effects, modes of action, and identification of effective biomarkers suitable for HPT disruption is possible. EDC-derived effects are likely to cascade into a plurality of physiological effects far more complex than the few variables tested within any research studies. The field should move towards understanding a system of hormonal systems' interactions rather than maintaining hormone system silos.

1. Introduction

1.1. Thyroid hormone functions and relevance

Thyroid hormones (THs) are important regulators of growth, development, and metabolism of all vertebrates (Forrest and Visser, 2013). TH signaling is essential for many KEY developmental processes across vertebrates including postembryonic metamorphosis in amphibians, lamprey, and flounder (Gilbert and Frieden, 1981; Manzon and Manzon, 2017; Schreiber and Specker, 1998; Shi, 2000; Thambirajah et al., 2019); smoltification of salmonids (Holzer and Laudet, 2015); molting in birds (McNabb, 2007); skin shedding in snakes (Chiu et al., 1983); and neurological development during the perinatal period in mammals including humans (Zoeller and Rovet, 2004; Zoeller, 2010). In addition, TH controls many essential physiological functions throughout life including thermoregulation in homeotherms (Frare et al., 2021; McNabb, 2000; Merryman and Buckles, 1998); thermal acclimation in zebrafish (Little et al., 2013); mood in humans (Hage and Azar, 2012); mating and foraging behavior in birds and reptiles (McNabb, 2000; Pajdak-Czaus et al., 2019; Rivera and Lock, 2008); hibernation in bears (Tomasi et al., 1998); cardiovascular function (Jabbar et al., 2017); and overall energy expenditure (Mullur et al., 2014) among others.

The fundamental processes influencing hormone metabolism and mechanisms of action are largely conserved across vertebrate species (Mullur et al., 2014) through the hypothalamus-pituitary-thyroid (HPT) axis (Fig. 1), although some differences have been reported between

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https://doi.org/10.1016/j.envres.2021.111906
Received 29 April 2021; Received in revised form 4 August 2021; Accepted 16 August 2021
Available online 18 August 2021

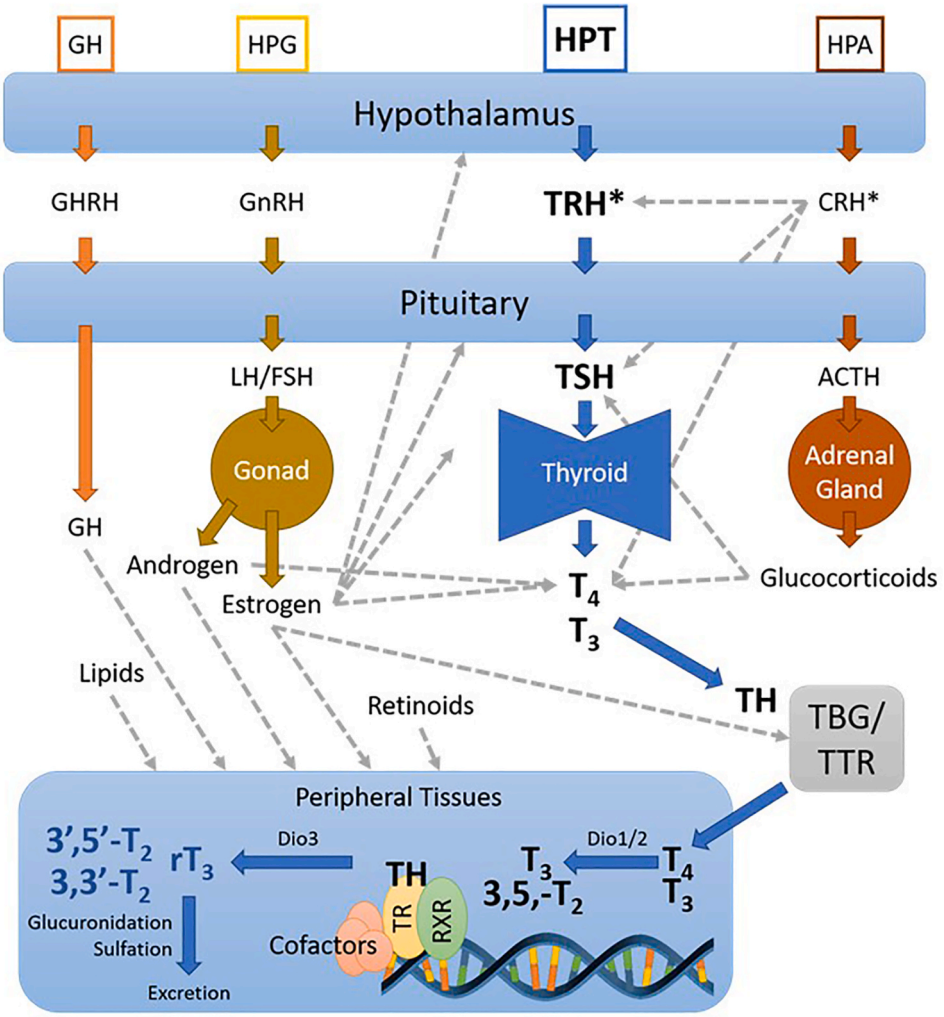

Fig. 1. Illustration of known influences of growth hormone (GH), hypothalamus-pituitary-gonad (HPG), and hypothalamus-pituitary-adrenal gland (HPA) axes on the hypothalamus-pituitary-thyroid (HPT) axis. The major hormones released from the various tissues are indicated and dashed grey arrows indicate components that have empirical evidence from at least one animal group to influence TH signaling. Bioactive TH forms include T_4 and Dio1/2-converted T_3 and 3,5-T_2 are shown in black that bind to nuclear TRs in peripheral tissues to regulate gene expression (shown as "TH"). Dio3 inactivates T_4 giving rise to rT_3 and 3′, 5′-T_2 or T_3 producing 3,3′-T_2 shown in blue. Note that many effects on peripheral tissues have not been mechanistically determined. See text for more details. ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; Dio, deiodinase; FSH, follicle stimulating hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; TBG; thyroxine-binding globulin; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone; TTR, transthyretin. *In amphibians and birds, CRH in the HPA axis also plays the role of TRH in the HPT axis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

animal groups (Fig. 1 and see below). The hypothalamus releases thyrotropin releasing hormone (TRH) in mammals or corticotropin releasing hormone (CRH) in non-mammals to stimulate the anterior pituitary to produce thyroid stimulating hormone (TSH) (Burger and Patel, 1977; Okada et al., 2007). TSH then stimulates TH production in the thyroid gland (Fig. 1). Derived from the amino acid tyrosine, the iodinated forms of THs, primarily 3, 3', 5-triiodothyronine (T_3) and thyroxine (T_4), are synthesized by the thyroid gland through active iodine transport into the gland *via* Na^+-iodide symporters (NIS encoded by the *slc5a5* gene) and thyroid peroxidase (TPO) activity on thyroglobulin. THs are transported *via* various blood proteins to peripheral tissues (e.g., albumin and mainly thyroxine-binding globulin (TBG) in mammals or primarily transthyretin (TTR) in fish, amphibians, birds, and reptiles).

THs enter cells *via* membrane transporters where, in the case of T_4, type 1 or 2 "outer ring" deiodinases, Dio1 and Dio2, respectively, remove an iodine to convert it to T_3. This triiododinated form then binds to nuclear receptors, TRα or TRβ, encoded by the *thra* and *thrb* genes, respectively, that regulate the expression of TH-responsive genes (Mullur et al., 2014) (Fig. 1). T_4 can also bind - albeit with lower affinity - to these TH receptors and recruit different cofactors, thereby enabling differential control of gene expression outcomes (Schroeder et al., 2014) and deiodination of T_3 to 3,5-diiodothyronine (3,5-T_2) produces an alternative bioactive ligand for TRβ (Mendoza et al., 2013). Deiodination of THs by a type 3 "inner-ring" deiodinase (Dio3) converts T_4 to reverse T_3 (rT_3) and 3′,5′-T_2 or T_3 to 3,3′-T_2 (Holzer and Laudet, 2015) (Fig. 1). These inactive forms are then transported to the liver for glucuronidation [by glutathione S-transferase (GST) or uridine 5′-diphospho-glucuronosyltransferase (UGT)] or sulfation followed by excretion in bile (Mullur et al., 2014) (Fig. 1).

1.2. TH signaling crosstalk with other hormonal systems

It is well-known that TH signaling influences production and signaling of multiple hormonal systems, including estrogen, androgen, growth hormone (GH), and glucocorticoids (GCs). This is in part due to shared tissue structures (e.g., hypothalamus, pituitary), common origin of hormone receptors, transcription cofactor sharing and overlap in the regulation of physiological processes. For example, it is hypothesized that thyroid function co-evolved with reproduction and that primitive TH function was associated with gonadal maturation (Norris and Carr, 2013). Studies with lamprey demonstrate that these ancient vertebrates exhibit a complex interplay between the HPT and hypothalamus-pituitary-gonadal (HPG) axis for the regulation of sexual maturation (Sower et al., 2009; Youson and Sower, 2001). Consequently, Sower et al. (2009) proposed that these axes evolved from an ancient axis that regulated development, metabolism, and reproduction. The interplay observed in contemporary animals among HPT and HPG axes may reflect the evolutionary history of these endocrine axes.

Indeed, direct crosstalk, where a component of a signaling pathway is shared by two or more signaling pathways, among the HPT and HPG axes is evident in all clades of vertebrates from fish to reptiles to mammals (Cooke et al., 2004; Cyr and Eales, 1996; Duarte-Guterman et al., 2014; Flood et al., 2013; Sun et al., 2016). Despite these

interactions among axes, the HPT and HPG axes are often studied independently, with the HPT axis mainly known for its role in metabolism, growth, and development while the HPG axis is well-known for its role in sexual development, reproduction, and behavior.

Additional crosstalk opportunities exist between the HPT axis and GH or hypothalamus-pituitary-adrenal gland (HPA) axes. In birds, growth rate depends on circulating T_3 that is controlled by an inhibitory feedback loop between T_3 and GH (Scanes, 2009) (Fig. 1). The impact of GC products of the HPA axes (see below) are dependent upon developmental stage and vertebrate group.

1.3. Effects of endocrine disrupting chemicals (EDCs) on intersecting TH and other hormonal pathways

As there are multiple levels of control over the HPT axis, including tissue-specific factors, a myriad of targets for endocrine disrupting chemicals (EDCs) to exert their effects have been identified. Some EDCs act as mimics or direct inhibitors of hormone action through direct binding to TRs and/or blood transport proteins, while others inhibit or stimulate deiodinase or TPO activity, or inhibit iodine transport into the thyroid gland (Gore et al., 2015). The chemical composition and classes of TH EDCs are broad, and many remain to be identified (Gore et al., 2015). These include a variety of pharmaceuticals and personal care product constituents, persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and other halogenated flame retardants, constituents of plastics such as bisphenol A (BPA) and phthalates, metals, nanoparticles, petroleum oil products, and pesticides. We refer readers to several comprehensive reviews that discuss various examples of EDCs affecting the HPT axis across taxa (Crofton, 2008; Gore et al., 2015; McNabb, 2007; Thambirajah et al., 2019; Zoeller, 2010). While reptiles represent an enormously important group, contaminant-induced effects on HPT axis regulation have received exceedingly limited attention (Rosenfeld et al., 2017; Sparling et al., 2010; Tan and Zoeller, 2007) (Fig. 2).

Given the extensive integration of the HPT axis with other hormonal processes, surprisingly little attention has been given to the influence that this crosstalk may have on EDC impact, specifically how disruption of other hormone pathways may indirectly influence the thyroid axis. Of the 2550 PubMed abstracts that specifically discussed THs and EDCs, less than one quarter examined the intersection between HPT and other axes (Fig. 2). Of these, 77% focused on mammals, 18% on fish, 6% on amphibians, 5% on birds, and only 2% on reptiles (Fig. 2). The present review explores this concept by critically examining research conducted in a broad range of vertebrate species. We particularly focus on hormones involved in reproduction, stress, and energy metabolism and identify crosstalk nodes that influence the HPT axis (Fig. 1) noting that most mechanistic information is from mammalian systems. There is an abundant literature about crosstalk between nuclear receptor-mediated signaling pathways. The generation of genome-wide DNA-binding profile of nuclear receptors revealed numerous functional and reciprocal regulatory interactions (George et al., 2011; Martens et al., 2011; Ratman et al., 2013). Unfortunately, these experiments are costly and labor-intensive largely due to the lack of genomics resources across vertebrate classes.

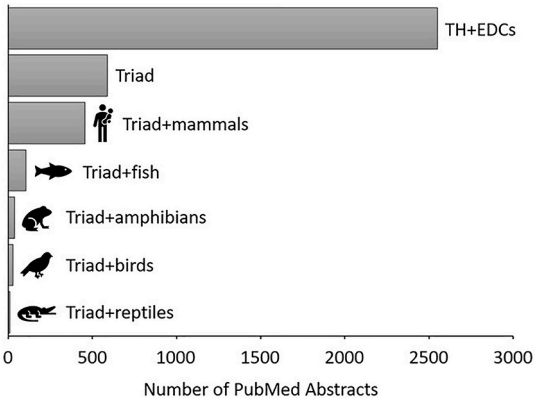

Fig. 2. Comparative analysis of studies published on crosstalk between TH signaling and endocrine pathways that are affected by endocrine disrupting chemicals by different vertebrate classes. Using the National Center for Biotechnology Information (NCBI) PubMed abstract search engine, the number of abstracts published for a given parameter were generated based on the following search terms: TH + EDCs: (Thyroid hormone) AND (endocrine disruption OR endocrine disruptor OR pollutant OR pollution). The "Triad" included TH + EDCs + intersecting axes (estrogens OR androgens OR glucocorticoids OR lipids OR retinoic acids). It is apparent that limited attention has been paid to vertebrate classes other mammals in the consideration of how intersecting endocrine regulation and TH signaling is affected by EDCs. Given the prevalence and multitude EDCs, understanding their effects on the crosstalk between hormonal systems is primed for further investigation.

2. Reproductive steroid hormones

Reproductive steroid hormones are the products of the HPG axis (Fig. 1) and are primarily produced by gonadal tissues – ovaries in females and testes in males. They are important in developing and maintaining sex characteristics and reproduction. The best studied reproductive hormones concerning EDCs are the estrogens and androgens (Delbès et al., this issue; Marlatt et al., this issue; Robaire et al., 2021).

2.1. Estrogens

2.1.1. Mammals

There is considerable evidence in the clinical and experimental literature of the impacts of pharmaceutical estrogens that exposure to estrogenic chemicals can alter thyroid physiology in mammals. While there is also a large literature showing changes in thyroid physiology due to exposure to non-pharmaceutical chemicals with estrogenic activity (e.g., bisphenol A [BPA], genistein), these chemicals have multiple mechanisms of action that might impair thyroid physiology independently of their interaction with estrogen-specific mechanisms. As such, it is not possible to disentangle the estrogenic-specific from the thyroid-specific actions. For example, soy formula consumption in infants is associated with impaired thyroid physiology (RIPP, 1961; Conrad et al., 2004; Fruzza et al., 2012) and in iodine-deficient rats (Kimura et al., 1976). Soy contains isoflavones such as genistein and daidzein that activate the nuclear estrogen receptors (ERs) (Hsieh et al., 1998; Kuiper et al., 1998) and induces estrogen-related physiological responses such as uterine hypertrophy, mammary gland growth and accelerating female puberty in rodents (Hsieh et al., 1998; Kanno et al., 2003; Thigpen et al., 2003). Genistein also inhibits rodent TPO activity *in vitro* and *in vivo* (Divi et al., 1997). To determine the extent to which estrogenic endocrine disruption may have on thyroid hormone signaling, we will therefore consider only the effects of physiological or pharmaceutical estrogens as these act in a highly specific manner on ERs. Their potency and specificity mean that they are unlikely to directly impact the well characterized molecular targets recognized as direct targets of thyroid disrupting chemicals (Murk et al., 2013).

Multiple important cell types that influence TH production are capable of responding to estrogens as various ERs are expressed in the thyroid gland (Santin and Furlanetto, 2011), pituitary (Stefaneanu et al., 1994), and hypothalamus (Suzuki and Handa, 2005). Normal thyroid follicular cells collected from fetal or adult humans express ERβ (Kawabata et al., 2003) raising the possibility that estrogens may influence thyroid gland development. It is notable that in many thyroid cancers and precancerous tumors, while ERα expression is maintained, ERβ is reduced compared to normal cells. In these cells, estrogen signaling through ERα promotes cell proliferation (Chen et al., 2008)

and the altered ratio of ERα to ERβ being directly correlated with more aggressive thyroid cancer (Mishra et al., 2020).

Sex differences in the incidence of thyroid diseases are evidence that gonadal steroids, in general, adversely impact human thyroid physiology. Population-wide studies consistently show that women have a higher risk than men for clinical hypo- or hyperthyroidism (Laurberg et al., 2006; Vanderpump et al., 1995), goiter (Malboosbaf et al., 2013; Vanderpump et al., 1995), thyroid nodules (Knudsen et al., 2000; Vander et al., 1968), and thyroid cancer (Davies and Welch, 2014; Hanai and Fujimoto, 1982; Ron et al., 1987). In particular, the maximal difference in incidences of thyroid cancer occurred in an age class corresponding to peak female reproductive years (i.e., maximum endogenous estrogen levels; age 25–34) where the incidence in women was seven times that observed in men of the same age (Ron et al., 1987). Intact female rats, but not ovariectomized females (with no endogenous estrogens), are also more susceptible to the experimental induction of thyroid cancer than males (Mori et al., 1990). However, administration of pharmacological estrogens to either ovariectomized females or castrated males increased their susceptibility to thyroid cancer (Mori et al., 1990). In addition, women consistently have higher incidence of circulating antibodies against thyroid epithelial cells (Hollowell et al., 2002; Knudsen et al., 1999; Loviselli et al., 1999; Pedersen et al., 2003).

The influence of estrogen on thyroid physiology in adult women has been recognized since at least the late 1940s when Heinemann and colleagues observed marked increases in protein bound iodine with pregnancy (Heinemann et al., 1948). Protein bound iodine was also increased in non-pregnant women by administration of pharmaceutical estrogens (Engstrom et al., 1952), while reduction of estrogens led to a marked increase in urinary excreted THs (Chan et al., 1972). Elevated serum total T_4 and T_3 (but not TSH or free T_4) were observed in women taking oral contraceptives compared to untreated women and men (Grüning et al., 2007) and in post-menopausal women receiving estrogen replacement therapy (Arafah, 2001). Changes in total T_4 and T_3 in response to estrogens is primarily due to an increase in circulating TBG. While estrogen does not directly increase hepatic TBG production, estrogens appear to increase the proportion TBG that is very highly glycosylated and resistant to degradation (Ain et al., 1987). Estrogen induced increase in TBG does not alter thyroid health in euthyroid women as TH production by the thyroid gland can compensate for increased serum pool of T_4 and T_3 (Tahboub and Arafah, 2009). However, in individuals where thyroid gland function is impaired, increased TBG can induce hypothyroidism (Tahboub and Arafah, 2009).

Estrogens can alter thyroid physiology through other mechanisms. Unlike most mammals and like non-mammals, post-natal rats do not express TBG and the major TH carrier protein in circulation is TTR. Yet studies in juvenile and ovariectomized rats reveal impacts of estrogens on the function of the HPT axis demonstrating that estrogens can exert influence on additional targets regulating TH production. For example, ovariectomy of adult female rats tends to reduce thyroid gland weight and modifies gland histomorphology (de Araujo et al., 2010; Marassi et al., 2007; Sosić-Jurjević et al., 2006). These impacts were reversed by treatment of these animals with pharmacological estrogens. Further, treatment of juvenile (prepubertal) or ovariectomized adult females with a low ("physiological") or high ("supraphysiological") dose of estradiol benzoate had little effect on circulating T_4 or TSH but caused increased thyroid gland weight, iodide uptake, and TPO activity (Lima et al., 2006). In the pituitary, studies with ovariectomized female rodents revealed that estrogens reduce the size of thyrotropes (Sosić-Jurjević et al., 2006) and suppressed TSHβ mRNA expression (Böttner and Wuttke, 2005), and amount of TSH protein (Boado et al., 1983). Adult female genetically modified mice that do not express ERα have higher mRNA expression of both α and β TSH subunits (Scully et al., 1997) in the pituitary gland compared with wild-type litter mates. This effect of the liganded ERα was shown to be mediated by interaction with transcription factor GATA2 which, in turn, inhibits expression of the human TSHβ subunit gene (Nagayama et al., 2008). Beyond the pituitary, estrogens also suppress hypothalamic TRH expression (Uribe et al., 2009). These observations may explain why estrogens can blunt the increase in TSH secretion in hypothyroid rats (Franklyn et al., 1987). In contrast, estrogens either have little impact (Grüning et al., 2007; Sawin et al., 1978; Tahboub and Arafah, 2009) or appear to increase TSH (Benvenga et al., 2017; Marqusee et al., 2000) in women.

Evidence that estrogen exerts effects independent of TSH come from studies of Ames dwarf mice in which pituitary thyrotropes fail to form in fetal development (Vidal et al., 2001). Thyroid glands in these mice have reduced thyroid follicle size but follicular epithelial cells still express proteins primarily regulated by TSH and express colloid into the follicle lumen. Chronic treatment with estradiol of ovariectomized adult female Ames mice resulted in marked further reduction in thyroid epithelial cell thickness and thyroglobulin immunoreactivity (Vidal et al., 2001). Treatment of thyroid progenitor cells, derived from human thyroid nodules, with physiologically relevant concentrations of estradiol cause these cells to proliferate but suppress the TSH-induced expression of NIS (Xu et al., 2013) suggesting a role for estrogen signaling in thyroid follicle differentiation. In contrast, thyrocytes from female rats have higher expression of peroxide generating enzymes (*Duox 1,2* and *Nox4*) than males and estradiol treatment of gonadectomized animals of either sex significantly increases thyroid gland expression of these enzymes (Stepniak et al., 2018). These studies suggest that physiologically relevant levels of estrogens can also influence the function of follicular cells of the thyroid gland.

Estrogens can therefore influence thyroid physiology in adult mammals *via* multiple mechanisms at the thyroid, pituitary, and hypothalamic levels as well as by altering the amount of carrier protein. As these mechanisms may help explain the higher risk of thyroid disorders in women, the relevance of these mechanisms for mediating thyroid effects of estrogenic chemicals is not clear. In each of these cases, the potency of estrogen required to induce these changes is considerable. However, the presence of physiological relevant levels of estrogen may increase susceptibility of females to the effects of thyroid disrupting chemicals. For example, in a population based survey in the US, urinary levels of NIS-inhibitor perchlorate are correlated with reduced T_4 and increased TSH in women but not men (Blount et al., 2006).

TH disruption during early life of humans and other mammals can have more significant, lifelong impacts on health particularly due to TH's essential role in mediating brain development. There is some evidence to suggest that fetal exposure to a modified endocrine environment of pregnancy immediately following ovarian hyperstimulation and oocyte retrieval of *in vitro* fertilization (IVF) cycles can have significant, persistent effects on thyroid physiology. Oocyte collection for IVF often involves hormonal treatment to recruit the growth and estrogen synthesis of many ovarian follicles. Circulating estradiol levels resulting from this can reach pathologically high levels and must be monitored daily to avoid circulatory crisis known as ovarian hyperstimulation syndrome (Blumenfeld, 2018). The extent to which thyroid physiology of women is altered during ovarian hyperstimulation, possibly due to excessive estrogens, remains inconclusive (Gracia et al., 2012; Mintziori et al., 2011). After oocyte retrieval each of the follicles that produced an oocyte will form a steroid hormone producing corpus luteum (CL). The human placenta produces gonadotropins during the first few months of pregnancy that stimulate the production of both progesterone and estradiol by the CL which, in turn, promote and maintain uterine support for the growing fetus. However, pregnancies that occur immediately following a cycle of ovarian hyperstimulation will be bathed in much higher levels of these steroids produced by many instead of the single CL that would normally support a singleton pregnancy (Lv et al., 2014). Circulating THs in children from these pregnancies - measured up to 10 years after birth - revealed abnormally elevated levels TSH, and free and total T_4 (Lv et al., 2014). Children from pregnancies initiated when thawed embryos were transferred to the uterus during cycles that did not involve ovarian hyperstimulation, exhibited levels of these hormone like those in children from medically unassisted pregnancies (Lv et al.,

2014). Maternal exposure of mice to high levels of estradiol during the first half of pregnancy leads to excess circulating T_4 in female offspring as well as higher TPO expression in the thyroid and critical transcription factor Pax8 in both sexes. This effect was greater in female pups where it persisted into adulthood (Lv et al., 2016). However, lifetime or *in utero* and early postnatal exposure of rats to moderate doses of estrogens (oral ethinyl estradiol) did not alter levels of circulating TSH, total T_4 and T_3 or any of several key aspects of brain development that are highly dependent on TH action in exposed pups of either sex (Bansal and Zoeller, 2019). Also noteworthy is the lack of any observed thyroid physiology effects observed in children born to mothers administered the potent estrogen diethylstibestrol (DES) during pregnancy despite intense scrutiny of diverse health outcomes in this large cohort (Troisi et al., 2013). Although some examples of long-term alteration in thyroid physiology have been reported following fetal exposure to high levels of estrogens, the literature is not universally supportive of this association. Moreover, the studies where changes in the HPT axis were observed involved fetal exposures to extremely high levels of potent estrogens. It is unclear if environmentally relevant exposures to estrogenic EDCs would generate sufficient levels of relevant estrogenic signaling to induce such effects.

2.1.2. Non-mammalian vertebrates

Comparatively little is known regarding estrogen effects on the HPT axis of non-mammalian vertebrates. Several studies on TH-dependent amphibian metamorphosis in Pipids and Ranids using 17β-estradiol or the synthetic estrogens, 17α-ethinylestradiol or DES, at physiological or supraphysiological levels, noted a decrease in the rate of metamorphosis (Brande-Lavridsen et al., 2010; Duarte-Guterman et al., 2014; Gray and Janssens, 1990; Hogan et al., 2008; Sharma and Patiño, 2010; Tompsett et al., 2012). When measured, no significant differences in total or free T_3 in plasma were observed (Brande-Lavridsen et al., 2010) despite competitive estrogen binding to Ttr (Yamauchi et al., 2000). Ethinylestradiol did not affect thyroid follicle volume or number, but did decrease follicular cell height (Brande-Lavridsen et al., 2010). Estradiol exposure did not affect the expression of classic TH-response genes including *thrb* and *thibz* and the expression of several thousand other genes in RNA-seq experiments (Bulaeva et al., 2015; Jackman et al., 2018). The mechanism for TH disruption remains unclear as do the extent of estrogenic effects. For example, not all species respond in the same way. In contrast to Pipids and Ranids, Bufonid exposure to estrone can accelerate tail regression in *Bufo bufo* (Frieden and Naile, 1955).

To our knowledge, correlational studies on fish examining the impact of EDCs on estrogen effects on the HPT axis are limited to goldfish and zebrafish. Adult male *Carassius auratus* were exposed to the organophosphate pesticide monocrotophos (Zhang et al., 2018b). A two-day exposure at 400 μg/L monocrotophos increased estradiol and T_4 levels, while no changes were observed for plasma T_3 levels. After 12 days, estradiol plasma levels were elevated in all treatments, while T_3 plasma levels were decreased at 40 and 400 μg/L. The authors speculated that the increased estradiol levels might be responsible for the modulation of hepatic deiodinases, notably a down-regulation of *dio2* and *dio3*.

In another study, adult female zebrafish (*Danio rerio*) were exposed to 300 μg/L agricultural fungicide, prochloraz (Liu et al., 2011) for up to 48 h. Prochloraz reduced estradiol and T_4 in plasma, while T_3 levels did no change throughout the experiment. The authors also reported a significant reduction of *tshb* mRNA in the fish brain that correlated with the decreased E_2 plasma levels.

While no relevant studies were reported in birds, in a study investigating the impact of embryonic sex steroid exposure on thyroid physiology in the American alligator (*Alligator mississippiensis*) from the EDC-contaminated Lake Apopka, results suggested that estradiol exposure did not impact thyroid physiology in these alligators (Galligan et al., 2019). This indicated that the effect of *in ovo* organochlorine pesticide exposure on the organization of the thyroid reported in a related study on this species (Boggs et al., 2013) was not mediated through estrogens.

Taken together, it is evident that mechanistic insights provided by the knowledge of TH-estrogen crosstalk primarily in mammalian systems can help address the wide modes of EDC action on these two axes and can guide hypotheses for testing in other vertebrates.

2.2. Androgens

2.2.1. Mammals

Although evidence that estrogens may drive much of the increased risk of thyroid disease among women compared to adult men, there is some evidence that androgens alter thyroid physiology in humans. Studies of endocrine changes that accompany androgenic anabolic steroid use show significant changes in circulating TH. Early controlled exposure studies revealed a significant reduction in plasma binding of T_4 in men (Rosenberg et al., 1962) suggesting reduced TBG. This was confirmed in more recent studies showing that anabolic steroid use in men is accompanied by reduced TSH, total and free T_4, total T_3, and TBG. All these reductions resolved to pre-steroid levels by four weeks after cessation (Alèn et al., 1987; Deyssig and Weissel, 1993). Similarly, women weightlifters using anabolic steroids exhibited clinically low serum TH binding capability (Malarkey et al., 1991).

Androgen treatment of transexual adults transitioning from female to male also exhibited a significant reduction in serum TBG after four months of testosterone treatment (Bisschop et al., 2006). These individuals also exhibit an increase in the ratio of T_3/T_4 suggesting higher deiodinase activity. Androgen antagonist (cyproterone acetate) treatments received by male to female transition patients caused a reduction of T_3/T_4 ratio but had not impact on TBG (Bisschop et al., 2006). More evidence comes from men unable to produce gonadotropins who received twice weekly human chorionic gonadotropin (hCG) treatments to stimulate testicular testosterone production. Serum T_4 was within the normal clinical range prior to hCG treatment but fell significantly after hCG treatment began and returned to pre-hCG levels after cessation of treatment (Spitz et al., 1983). TBG, T_3, and TSH were unaffected (Spitz et al., 1983). These results suggest that physiologically relevant exposures to androgens may affect adult thyroid physiology, but the nature of this effect remains to be determined.

Orchiectomy (Orex) and androgen treatment studies in adult male rats have provided more detailed evidence that androgens can influence TH physiology through several mechanisms. For example, Orex adult male rats have reduced serum TSH, TSH receptor concentration, and TSH binding to thyrocytes (Banu et al., 2001a, 2001b). Androgen treatment of Orex rats restored these three parameters (Banu et al., 2001a, 2001b) and pituitary *tshb* expression to levels observed in intact male rats (Ross, 1990). Even in mice with TSH-secreting pituitary tumors with serum TSH levels 1000-fold excess that found in normal mice, testosterone treatment increased serum TSH by ~70% (Ross, 1990). Orex rats also have reduced *trh* mRNA and protein in hypothalamus and pituitary, respectively, which is restored to levels in intact rat with testosterone treatment suggesting androgens act at least in part on TRH-secreting cells (Pekary et al., 1990). Also in rats, androgens influence thyroid epithelium directly as androgen receptors (ARs) are expressed in thyroid epithelial cells of both sexes (Banu et al., 2002). These cells proliferate more rapidly in immature male compared to female rats and peak proliferation rate in male rats coincides with a maximum AR expression in thyroid cells and a pre-weaning peak in circulating testosterone around postnatal day 10 (Banu et al., 2001b, 2002). Orchiectomy caused no change in serum TSH or T_4 but caused a reduction in cross sectional area of thyroid follicles and colloid density, suggesting reduced activity (Sosic-Jurjevic et al., 2012). In addition, a reduction in orchiectomy-induced hepatic Dio1 and pituitary Dio2 activity were reversed by testosterone treatment (Sosic-Jurjevic et al., 2012). Similarly, androgen treatment also limited the reduction in total and free T_4 and the increase in serum TSH observed in Orex male rats that was induced by a low iodine diet (Bahrami et al., 2009). These

studies suggest that androgen reduces TSH expression.

All the above responses of TH physiology were induced by doses of androgen that were equivalent or higher than normal androgen levels in adult males. Moreover, most EDCs that interact with androgen physiology leading to adverse effects tend to be inhibitors rather than activators (Gore et al., 2015). While these EDCs may have significant impacts on male reproductive development when exposure occurs during the critically sensitive masculinization programming window (Delbès et al., this issue; Gore et al., 2015; van den Driesche et al., 2017), there is very little information on the potential for developmental exposures to antiandrogenic chemicals to alter thyroid physiology.

2.2.2. Non-mammalian vertebrates

There is some evidence of the interaction of androgen signaling and thyroid physiology in non-mammalian vertebrates. Insight into a mechanistic basis for androgen crosstalk has come from amphibian studies (Flood and Langlois, 2014). The steroid 5α- and 5β-reductase (srd5α and srd5β) enzymes are essential in the final steps of androgen biosynthesis (Robitaille and Langlois, 2020) while the enzyme aromatase (Cyp19, encoded by the *cyp19* gene) is responsible for estrogen biosynthesis (Simpson et al., 1994). In a series of studies with *Silurana (Xenopus) tropicalis*, researchers investigated the effects of Srd5 inhibition by finasteride exposure and Cyp19 inhibition by fadrozole exposure on amphibian development. Finasteride is used to treat hair loss and is part of hormone therapy for transgender women (Hu et al., 2019) and fadrozole is used in breast cancer treatment (Kharb et al., 2020). Chronic larval exposures to finasteride and fadrozole from early embryonic stages through metamorphosis were performed to investigate gene expression effects on brain (Langlois et al., 2011) and liver (Duarte--Guterman et al., 2009), or whole embryos through to feeding tadpoles (Langlois et al., 2010). Both treatments resulted in intersex individuals (Duarte-Guterman et al., 2009; Langlois et al., 2011) and alterations in TH-related gene expression. For example, when exposed to finasteride, phenotypic males had increased *thrb* expression in the liver (Duarte--Guterman et al., 2009) and brain (Langlois et al., 2011) compared to controls. Intersex animals also had an increase in brain *thrb* expression (Langlois et al., 2011). Males and intersex individuals had an increase in their hepatic *dio2* expression and a decrease of hepatic *dio3* (Duarte--Guterman et al., 2009). However, in both males and intersex individuals, brain *dio3* expression was increased (Langlois et al., 2011). In whole larvae, both *dio1* and *dio2* mRNA expression was decreased (Langlois et al., 2010). Such results suggest that finasteride -treated males and intersex animals could be increasing their active TH concentration to counteract the effects of finasteride. Such conclusions come also from the fact that THs seem to be involved in male development, as observed in some fish (Goleman et al., 2002; Mukhi et al., 2007). Exposure to fadrozole did not elicit effects on the TH machinery in the liver or brain (Duarte-Guterman et al., 2009; Langlois et al., 2011). However, in whole larvae, both *thra* and *thrb* mRNA levels increased relative to controls, while *dio1* and *dio3* transcripts decreased and increased, respectively.

In an investigation using *S. tropicalis,* Karlsson et al. (2021) assessed the multigenerational effects of linuron, an anti-androgen pesticide on amphibian reproduction, metabolism and development. The authors exposed frogs to ~30 μg/L linuron, a phenylurea herbicide, from the late embryo stage until the completion of metamorphosis. Both F_0 males directly exposed to linuron and male F1 and F2 offspring presented perturbation in the reproductive system (decreased fertility) and in their thyroidal system (alteration in the hindlimb length). Such phenotypic outcomes are a possible down-stream effect of AR and TR antagonism as molecular initiating events from this EDC (Karlsson et al., 2021). The authors also suggested that the adverse outcomes observed in *S. tropicalis* after linuron exposure might be the result of an interaction of the HPT and HPG axes.

In some cases, testosterone levels were measured in tandem with estrogenic end points in studies mentioned in Section 2.1. For example, *C. auratus* exposed to monocrotophos exhibited reduced plasma testosterone levels at 40 and 400 μg/L (Zhang et al., 2018b) and *D. rerio* exposed to prochloraz exhibited reduced plasma testosterone levels at 300 μg/L (Liu et al., 2011). Analyses from Lake Apopka alligators demonstrated that embryonic androgen (dihydrotestosterone) exposure did not impact thyroid physiology (Galligan et al., 2019). This indicated that the effect of *in ovo* organochlorine pesticide exposure on the organization of the thyroid reported in a related study on this species (Boggs et al., 2013) was not mediated through steroid hormones. The authors could therefore not conclude that thyroidal physiology in the American alligator is sensitive to steroid hormone signaling at early life stages.

In a study of the lizard *Podarcis bocagei* exposed in the field to a mixture of herbicides (major compounds detected were alachlor, bentazone, dicamba, dimethenamid-p, mesotrione, and terbuthylazine), it was reported that the thyroid gland was significantly more active in lizards from the exposed sites, and that there was an up-regulation in TR expression in testes of these lizards (Bicho et al., 2013). In a study of *P. sicula*, Cardone et al. (2000) demonstrated that the induction of AR mRNA was regulated by testosterone and T_3 independently. As a result, increased levels of T_3 would increase the expression of AR mRNA (Cardone et al., 2000), thereby making Sertoli and germ cells more responsive to circulating testosterone. Bicho et al. (2013) therefore suggested that in *Podarcis bocagei*, premature commencement of spermatogenesis in lizards exposed to herbicides (not observed in lizards from the reference sites), was through the induction of AR mRNA, as a predictable consequence of higher thyroid gland activity and upregulation of TRs. Nevertheless, the authors concluded that it remains unclear if these effects affect the long-term viability of *P. bocagei* populations (Bicho et al., 2013).

These results suggest that androgens can influence the HPT axis across vertebrate species. The precise relationships, mechanisms, and physiological consequences remain to be determined.

3. Glucocorticoids (GCs)

Produced in the adrenal cortex, GCs are a class of corticosteroid hormones that bind to the glucocorticoid receptor (GR) that are ubiquitously found in vertebrate cells (Pelt, 2011). The GCs, corticosterone and cortisol, mediate physiological responses to stress including cardiovascular effects, suppression of the immune system and inflammation, in addition to diverse metabolic and homeostatic changes. Regulation through the HPA axis shares a special connection with the HPT axis in some vertebrates because CRH regulates both axes (Fig. 1). Alterations of CRH expression (De Groef et al., 2006) are predicted to translate into strong downstream effects in both pathways. Moreover, in birds and frogs, CRH displays thyrotropic activity (Denver, 1993; Watanabe et al., 2018). Thus, changes in CRH expression are a key marker of crosstalk alterations. In most studies reporting alterations of both CRH expression and various components of TH signaling, the experimental design is not geared toward directly addressing the crosstalk between the two pathways. CRH is used to interrogate HPT axis status and the HPA axis is explored only rarely. Most of the time, quantitative measures of hormones levels are not provided, but when they are, they almost always correspond to T_3 and T_4, as cortisol and corticosterone received much less attention.

3.1. Mammals

The potential impacts of fetal mammalian exposure to GCs on the maturation and function of the HPT axis has important clinical implications as synthetic GCs (e.g., dexamethasone) are administered to pregnant women when premature birth is anticipated. As GCs are essential for promoting the maturation of lungs, this therapy greatly improves lung function and, consequently the survival of premature infants (Roberts and Dalziel, 2006). Prenatal GC exposure may also accelerate maturation of the HPT axis. In infants born prematurely (<34

weeks gestation), those whose received antenatal GC treatments had lower serum TSH, lower incidence of very high TSH levels (>15 mIU/mL) and of exaggerated responses to TRH challenge compared to similar infants who were not treated of did not receive a treatment with prenatal GC (Hanaoka et al., 2020). Postnatal GC treatment of early premature infants to improve lung function, suppressed TSH and T_3 levels and increasing rT_3 (Arai et al., 2009; Buimer et al., 2008). Notably, TSH rebounded after withdrawal of GC treatment to exceed that seen in untreated premature infants of comparable age (Arai et al., 2009).

Studies in sheep suggest that the late pregnancy surge in fetal adrenal GC secretion drives the late fetal increases in circulating T_3 and Dio1 activity in multiple tissues, and a decrease in placenta and kidney Dio3 (Forhead et al., 2006). Maternal ovine GC treatment, similar in dose and frequency used in threatened premature birth, increased TH levels plus fetal hepatic Dio1 and Dio3 activity (Forhead et al., 2007). GC exposure of female rats in late pregnancy led to a decrease in number of TSH-containing cells in the fetal pituitary at term (Manojlovic--Stojanoski et al., 2010). Early life GC exposure modulates deiodinase expression in several tissues. For example, exposure of the rat fetus (at 20 days of gestation) to GC led to a reduction in liver and kidney Dio1 and Dio3 activity, an increase in Dio2 activity in the brain but did not influence circulating total T_4 or T_3 (Van der Geyten and Darras, 2005). In contrast, early postnatal GC exposure (postnatal day 5) had no effect on hepatic or kidney Dio1, increased Dio3 in both tissues, increased Dio2 in brain and reduced circulating total T_4 and T_3 (Van der Geyten and Darras, 2005). In addition, different levels of fetal GC exposure from the maternal circulation can lead to very long-term changes in TH physiology. Maternal adrenalectomy during mid gestation resulted in increased fetal adrenal activity *in utero*, elevated fetal GC, increased plasma TSH, and decreased TRH and T_3 in the affected pups as adults (Slone-Wilcoxon and Redei, 2004). Implantation of pregnant dams with GC releasing pellets at the time of adrenalectomy reversed this effect suggesting that maternal GCs can modulate the fetal HPT axis potentially leading to lifelong consequences.

In adult mammals, GC signaling influences many aspects of energetic metabolism in a broad range of tissues. Part of this influence is due to effects on the HPT axis. In most human patients with pathologically high GC levels (Cushing syndrome), circulating TSH, free T_4 and T_3 are suppressed as is the nocturnal surge in TSH levels but these tended to return to normal after treatment of the disease (Shekhar et al., 2021). GC administration to healthy adults reduced circulating TSH and T_3 levels and blunted the increase in TSH induced by TRH-administration (Re et al., 1976). Diurnal variation in Dio2 activity in vascular smooth muscle in rats correspond with changes in corticosterone levels in rats with the lowest levels of aortic Dio2 activity coinciding with peak levels of circulating corticosterone (Toyoda et al., 2009). This circadian reduction in Dio2 was blocked in animals treated with corticosterone synthesis inhibitor, metyrapone, while treatment with dexamethasone reduced Dio2 activity (Toyoda et al., 2009). Similarly, acute stress in rats resulted in prolonged increase in GC secretion and this was associated with a reduction and disruption of circadian changes in circulating TSH (Martí et al., 1996). These data suggest that exogenous or endogenous GC exposure can alter thyroid physiology. While the potency of GC required to induce these effects suggest that it unlikely that GC-like activity of exogenous chemicals (other than GC-like drugs) will disrupt thyroid physiology, chronic stress may render organisms more sensitive to adverse effects of substances acting *via* specific thyroid disrupting mechanisms.

3.2. Non-mammalian vertebrates

The importance of crosstalk between HPT and HPA axes cannot be understated as it is necessary for survival. Recent work with proopiomelanocortin (*pomc*)-knockout *S. tropicalis* tadpoles that do not produce ACTH clearly demonstrated perturbed TH signaling through reduced growth rates and development, with lower expression of the TH-response genes, *klf9* and *thrb* (Shewade et al., 2020). Acceleration of metamorphosis by exogenous TH administration was only rescued in the presence of exogenous corticosterone, and was required to prevent deaths that occurred during TH-induced tail resorption (Shewade et al., 2020).

Even low levels of synthetic GC display strong toxicity for aquatic species (Chen et al., 2017) Significant quantities of dexamethasone and other synthetic GC agonists/antagonists are found in aquatic environments, with levels up to 900 ng/L in the Thames River in the United Kingdom (Kugathas et al., 2012) and up to 23 mg/L in wastewater in France (Creusot et al., 2014). In fact, they are found in nearly all anthropized environments. Given the functional crosstalk between TH and GC pathways, imbalance between TH and GC levels and/or expression level of their corresponding target genes can be used as indicators of perturbations.

Dexamethasone, at environmentally relevant doses, strongly affect *Xenopus* metamorphosis through a complex mechanism altering prolactin expression, which is thought to mediate this effect. The expression level of *dio3* is also reduced, but with little or no effect on *thrb*, *dio1*, and *dio2* expression (Lorenz et al., 2009). The detailed mechanism is not known. Another poignant example of this crosstalk is in T_4-induced metamorphosis of the neotenic axolotl, *Ambystoma mexicanum*, where dexamethasone or CRH synergizes with a submetamorphic dose of T_4 to promote Dio2 activity in the brain, leading to metamorphosis induction. The same dose of T_4 alone did not induce metamorphosis (Kuhn et al., 2005).

The anuran *Rhinella arenarum* displays strong histological and morphological abnormalities when exposed to dexamethasone (Cuzziol Boccioni et al., 2021), together with a reduced GST activity in the liver. Although the precise mechanism needs to be properly addressed, altered GST activity in the liver has been proposed to indicate a possible imbalance of TH signaling (Kelley and Bjeldanes, 1995). It is not clear whether this is a direct effect of dexamethasone on liver activity or an indirect consequence of developmental defects.

As mentioned at the beginning of this section, perturbations in *crh* gene expression can conceivably result in a change in HPA and HPT signaling. Indeed, studies from fish and amphibia report such observations for a wide range of EDCs (Table 1). It must be stressed however that these observations were disproportionately obtained from zebrafish embryos and the impacts on other vertebrates and developmental stages have yet to be evaluated. In some cases, an indirect mechanism of disruption is suspected. For example, repression of HPA and HPT pathways by pentabromobenzene is thought to be indirect since several genes are differentially regulated including those of the prolactin pathway (Peng et al., 2020).

In addition to gene expression biomarkers, there are also indications of complex interplays between HPT, HPA, and HPG axes because of pesticide exposure. Zhang and colleagues addressed the impact of synthetic pesticides (λ-cyhalothrin, fenvalerate, and permethrin) on several nuclear receptor signaling pathways in zebrafish embryos (Zhang et al., 2017b). Yhey showed that T_3 levels are always reduced, as well as *thr α* and *thr β* expression, which is a clear sign of TH disruption. Also, they found that *GR* expression is either up or down regulated depending on the compound and that *AR*, *ER*, and mineralocorticoid receptor expression were also affected. This illustrates the complex interplay between signaling pathways and the potential havoc created by EDCs.

This work was later followed by additional investigations in zebrafish embryos addressing the synergistic action of pesticide cocktails, with beta-cypermethrin and thiacloprid (Shen et al., 2021; Zhang et al., 2017b), or myclobutanil and thiamethoxam (Wang et al., 2020). The experimental design was similar, and they both showed alterations of gene expression of the HPT axis (*tsh, dio1, crh*) or HPA axis (*ckcl, bax, crh*). The toxicity of each mixture was found to be much higher than each individual compound, clearly showing the damaging effect of their synergy.

Table 1
Summary of gene expression and hormone endpoint crosstalk between the HPT and HPA axes in representative non-mammalian vertebrates. ↑, increase relative to control; ↓, decrease relative to control; ↔, no change relative to control; -, not determined.

			Gene Transcript																					Hormone			
EDC	Species	Source	*crh*	*pomc*	*gr*	*thra*	*thrb*	*tshb*	*trh*	*dio1*	*dio2*	*dio3*	*slc5a5*	*tg*	*ttr*	*ugt*	*ar*	*er1*	*er2a*	*er2b*	*ahr1*	*ppara*	*pxr*	T_3	T_4	GC	Reference
Flame retardants																											
Hexabromocyclo-dodecanes (HBCD)	*Danio rerio*	larvae	↓	–	–	↓	–	–	–	↔	↔	↔	↔	–	↔	↔	–	–	–	–	–	–	–	↓	↓	–	Guo et al. (2019)
Pentabromo-benzene (TBB)	*Danio rerio*	larvae	↑	↑	↔	↔	↔	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓	–	–	Peng et al. (2020)
Polybrominated diphenyl ether	*Rana (Lithobates) pipiens*	tadpole	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓	↔	↑	Freitas et al. (2017)
2,2,4′,4′-Tetrabromo-di-phenyl ether (BDE-47)	*Danio rerio*	F1 embryos	↑	–	–	–	–	↑	–	↑	–	–	–	↑	↓	↑	–	–	–	–	–	–	–	↑	↓	–	Zhao et al. (2016)
2,4,6-Tribromophenol (TBP)	*Danio rerio*	larvae	↓	–	–	↓	↓	↓	↓	↓	↓	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Fu et al. (2020)
Triphenyl phosphate (TPP)	*Danio rerio*	adult male brain	↑	–	–	–	–	↑	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓	↓	–	Liu et al. (2019b)
Triphenyl phosphate (TPP)	*Danio rerio*	adult female brain	↓	–	–	–	–	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↑	↑	–	Liu et al. (2019b)
Triphenyl phosphate (TPP)	*Danio rerio*	male embryo	–	↑	–	–	–	–	↔	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↑	↑	↓	Liu et al. (2016)
Triphenyl phosphate (TPP)	*Danio rerio*	female embryo	–	↔	–	–	–	–	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↔	↔	↑	Liu et al. (2016)
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	*Danio rerio*	adult male brain	↑	–	–	–	–	↑	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓	↓	–	Liu et al. (2019b)
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	*Danio rerio*	adult female brain	↓	–	–	–	–	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↑	↑	–	Liu et al. (2019b)
Plasticizers																											
Bisphenol F	*Danio rerio*	embryo	↑	–	–	–	–	–	–	–	↑	–	↑	↑	↓	–	–	–	–	–	–	–	–	↑	↓	–	Huang et al. (2016)
Bisphenol S	*Danio rerio*	embryo	↑	–	–	–	–	↑	–	↑	↑	–	–	↑	–	–	–	–	–	–	–	–	–	↓	↓	–	Zhang et al. (2017a)
Surfactants																											
Perfluoroalkyl phosphinic acids (PFPiAs)	*Danio rerio*	embryo	↑	–	–	↑	↑	↑	–	↑	↑	–	–	–	↑	↑	–	–	–	–	–	–	–	–	–	–	Liu et al. (2019a)
Perfluoro-dodecanoic acid (PFDoA)	*Danio rerio*	embryo	↑	–	–	↓	↓	↓	↑	↑↓	↑	–	↓	↓	↓	–	–	–	–	–	–	–	–	–	–	–	Zhang et al. (2018a)
Polychlorinated biphenyls (PCBs)																											
Aroclor 1254	*Sparus aurata*	juvenile	↑	–	–	–	–	–	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↑	Skrzynska et al. (2019)
Pesticides																											
Atrazine	*Ambystoma tigrinum*	larvae	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		↑	↓	Larson et al. (1998)
λ-Cyhalothrin	*Danio rerio*	embryo	–	–	↑	↓	↓	–	–	–	–	–	–	–	–	–	↓	–	↓	↓	↑↓	↑	↑	↓	–	–	Zhang et al. (2017b)
Fenvalerate	*Danio rerio*	embryo	–	–	↓	↓	↓	–	–	–	–	–	–	–	–	–	↓	–	↑	–	↑	↑	↑	↓	–	–	Zhang et al. (2017b)
Fluoride	*Scophthalmus maximus*	juvenile	↑	–	–	–	↑	↑	↑	↑	↑	–	↑	–	↑	–	–	–	–	–	–	–	–	↑	–	–	Jianjie et al. (2016)
Glyphosate and commercial preparations	*Xenopus laevis*	tadpole brain	↓	–	↓	–	↓	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	Lanctôt et al. (2014)
Nitrates	*Scophthalmus maximus*	juvenile	↑	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	↓	↓	↑	Yu et al. (2021)
Permethrin	*Danio rerio*	embryo	–	–	↓	↓	↓	–	–	–	–	–	–	–	–	–	↓	↑	↑	↑	↑	–	↑	↓	–	–	Zhang et al. (2017b)
Triphenyltin (TPT)	*Danio rerio*	embryo	↑	–	–	↓	↓	↑	–	↓	↓	–	–	↑	–	–	–	–	–	–	–	–	–	↓	↓	–	(Li et al., 2019; Yao et al., 2020)

Dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) are strong HPG and HPT axis disruptors, which also affect *crh* expression (Wu et al., 2019). In goldfish (*Carassius auratus*), monocrotophos pesticides are potent TH disruptors, that also lower *crh* expression in female (Zhang et al., 2014). Dimecron reduces endogenous levels of T_3 and cortisol in *Sarotherodon mossambicus* (Thangavel et al., 2005).

Complex mixtures of contaminants also show indications of potential crosstalk. Zebrafish embryos exposed to gangue from coal mining sites display developmental abnormalities and strong disruption of HPT axis gene expression together with *crh* expression (Yang et al., 2019). In *Sparus aurata*, juveniles exposed to contaminated marine sediments display alterations of *thr* and *gr* expression, together with *mtt, cyp3* and *hsp7*0 that are indicators of stress response (Ribecco et al., 2011). This may be indicative of altered crosstalk and, although this study is based on micro-arrays experiments, the full dataset is not described, and it is not possible to look for additional effects.

In summary, crosstalk of the HPA and HPT axes can occur at multiple levels. In non-mammals, the relationship is very clear as both pathways share the same pituitary hormone (CRH). Further investigation is needed at the cellular receptor level where transcriptional cofactors may be shared between the GR and TR complexes.

4. Retinoids

Retinoids are essential factors regulating the development and function of many organs and physiological processes (Das et al., 2014; Ghyselinck and Duester, 2019). Retinoid functions are primarily mediated by multiple isomers of retinoic acid (RA) that bind to and activate the retinoic acid receptor (RAR) family of nuclear receptors and the retinoid X receptor (RXR). Liganded RARs form heterodimers with RXR and this binds directly with specific DNA elements in regulated genes to control transcription. RXR also forms heterodimers with many other members of the nuclear receptor superfamily – including TRs. RA influence on transcriptional activity of THR-RXR is inconsistent and context dependent (Castillo et al., 2004; Li et al., 2002; Mengeling and Furlow, 2015). For example, RA can stimulate the expression of a TH response element (TRE)-linked reporter gene and multiple TRE regulated genes in GH3 rat pituitary cells *in vitro* (Mengeling and Furlow, 2015). In contrast, this thyroid responsive construct was not transcribed by RXR ligands in liver cell lines, nor were TRE-regulated genes altered by RA in pituitary cells, suggesting that THR-RXR transactivation by RXR ligands is dependent on cell type. The RXR is suspected of being particularly important for the repressive action on genes for which TH exerts expression inhibition (Laflamme et al., 2002). Also, RA stimulates the dissociation of corepressor complex from the THR-RXR heterodimer in the absence of T_3, but does not increase association with co-activator complex (Fattori et al., 2015). This suggests that the liganded RXR may alleviate the repressive effect of the unliganded THR-RXR on gene transcription but is insufficient to initiate transcriptional activation. As such, a chemical with affinity for the RXR may alter thyroid hormone signaling to a limited extent in some contexts, although it is unclear to what extent this might alter TH physiology.

Although retinoids are essential for the normal development of many vertebrate organ systems, especially during early tissue differentiation (Das et al., 2014), retinoids have primary roles in the formation and differentiation of the thyroid gland in mammals (De Felice and Di Lauro, 2011). In contrast, there is ample evidence that retinoids modify thyroid physiology in mammals. It has been recognized since the 1930s that excess vitamin A can suppress the effects of excess TH in rodents and humans [(Logaras and Drummond, 1938) and references cited therein]. Vitamin A deficiency increases the incidence and severity of thyroid gland hypertrophy (goiter) and degree of serum TSH elevation among iodine deficient children (Zimmermann, 2007; Zimmermann et al., 2004). In addition, altered TH status has been reported in adults receiving potent retinoids to treat several conditions (e.g., lymphoma, severe acne, psoriasis). Exposure to RAR-selective [acitretin (Angioni et al., 2005); isotretinoin (Karadag et al., 2011; Masood and Hakeem, 2011)] or RXR-selective [bexarotene (Graeppi-Dulac et al., 2014; Sherman et al., 1999);] drugs cause reduction in circulating TSH leading to clinically-relevant central hypothyroidism in extreme cases (Sherman et al., 1999).

Animal studies have been used to identify the specific site(s) of retinoid action in altering HPT axis function. Rats with vitamin A deficiency but normal iodine status, had elevated pituitary TSH levels and elevated TRH in the hypothalamus relative to paired controls (Morley et al., 1978). This was associated with elevated pituitary expression of the *tshb* subunit that was reduced to control levels by treatment with all *trans* retinoic acid (Breen et al., 1995). Other studies, however, showed that vitamin A deficiency only influenced circulating TSH and pituitary *tshb* subunit expression in iodine-deficient rats, but not iodine-sufficient animals (Biebinger et al., 2006, 2007). Synthetic retinoids that specifically activate RXR, but not RAR, also suppress *tshb* gene expression in mouse pituitary *in vivo*, leading to central hypothyroidism like retinoic acid treatment (Sharma et al., 2006). In rats, this treatment caused reduced circulating T_3, T_4 and TSH and TSH response to a TRH challenge *in vivo* (Liu et al., 2002). This is consistent with elevated levels of circulating TSH and T_4 in RXRγ mice (Brown et al., 2000) and the hypothyroid action of RXR-specific pharmaceuticals in human subjects (Graeppi-Dulac et al., 2014; Sherman et al., 1999). Given that reduced expression and secretion of TSH is a classical response to T_3 activation of TRβ in the thyrotrope and that TRβ acts as a heterodimer with RXR, this supports the hypothesis that RXR specific agonists may be acting *via* this heterodimer complex. This is inconsistent with the observation that RXR-specific agonists are equally potent in reducing TSH expression in both wild type and TRβ knock-out mice (Macchia et al., 2002), demonstrating that TRβ is not required for the full expression of RXR effects. This suggests that the suppressive effects of retinoids on pituitary thyrotropes are mediated *via* the effects of RXR as a heterodimer of a permissive nuclear receptor.

Retinoic acid receptors are expressed in thyroid epithelial cells, which retinoids can directly influence (del Senno et al., 1994; Schmutzler et al., 2004). Treatment of porcine thyrocytes *in vitro* with retinol inhibited TSH-induced iodide uptake and reduced T_4 and T_3 release (Arai et al., 1991). Retinoic acid potently inhibited TSH-induced expression of *Tpo* and *Tg* in human thyroid epithelial cells (Namba et al., 1993). These studies suggest that retinoids tend to inhibit activity in differentiated primary thyroid epithelial cells (Schmutzler et al., 1997).

In contrast, retinoid treatment of thyroid cancer cells tends to induce functions typical of differentiated thyroid cells. Exposure of thyroid epithelial carcinoma cells to RA reduced cell proliferation, increased TSH receptor numbers and induced a 4-fold increase in iodide uptake (Van Herle et al., 1990). A second study confirmed that RA induced increased *Slc5a5* gene expression in some thyroid cancer cells, but reduced *Slc5a5* expression in differentiated thyroid cells (Schmutzler et al., 1997). RA may provide a valuable therapy for thyroid cancer as it enhances the vulnerability of tumor cells to radioactive iodine while reducing the uptake, thus sparing wild-type thyroid cells. A minority of patients treated with retinoids in clinical trials showed improved radioactive iodine uptake, but with no appreciable effect on tumor size (Pak et al., 2018).

These observations revealed how retinoid signaling can alter thyroid physiology in mammals and humans with adverse consequences, particularly for organisms susceptible to direct-acting thyroid EDCs. The vulnerability of RA and TH signaling interactions to EDCs are further exemplified by a study of the effects of propylthiouracil (PTU) on craniofacial development in zebrafish (Bohnsack et al., 2011). RA is a key mediator of craniofacial development and acts as a morphogen and teratogen when added to the media. Transgenic zebrafish lines expressing green fluorescent protein (GFP) in the neural crest or differentiated muscles exposed to 0.003% PTU modulates the RA

regulation of craniofacial development and decreased T_4 in nasopharynx thyroid follicles. Moreover, exogenous T_3 and T_4 administration partially ameliorated neural crest abnormalities caused by PTU (Bohnsack et al., 2011). PTU also blocks the strong teratogenic effects of RA added at high concentration (100 nM) into the media. This crosstalk would be partially mediated by insulin-like factor (IGF) signaling.

Arsenic disrupted both RA- and TH-mediated gene regulation in *Xenopus* cell-based luciferase reporter assays (Davey et al., 2008). Using a *Xenopus* tail regression test [cultivated *ex vivo* explants regress autonomously upon TH exposure (Tata et al., 1991)] tail regression was partially blocked by arsenic exposure. Although this clearly illustrates TH signaling disruption, this experiment provided no information relative to RA signaling.

The *Xenopus* tail regression test was independently employed to address the effects of BPA, which impeded T_3-induced resorption and reduced *thra* and *thrb* mRNA abundance (Iwamuro et al., 2006). Moreover, BPA blocked T_3-dependent autoinduction of *thra* and *thrb* (Iwamuro et al., 2006). Both T_3 and BPA moderately repressed *rxrg* expression, but this effect is not additive and there is no apparent synergistic or antagonistic action between the two molecules. These results emphasize the need to understand the effects of BPA, and other EDCs, on TH- and RA-signaling crosstalk.

Consideration of retinoid crosstalk with TH signaling has revealed clear mechanistic modes whereby EDCs can interfere with the HPT axis, particularly at the nuclear receptor and transcriptional complex level. Further inquiry into these modes of action across all vertebrate classes is warranted.

5. Lipids

Post-embryonic anuran development entails the coordinated and systematic remodeling of tissues and organs as tadpoles metamorphose into juvenile froglets. These complex morphological changes are instigated primarily by the endogenous production of THs, and yet involve more than the development of adult organs; the loss of tadpole phenotypes, such as through tail resorption, occur as well. Such seemingly contradictory gain and loss of attributes clearly speak to the requirement for TH-dependent activities to be fine-tuned through intersecting molecular activities.

Studies on the metabolite changes that occur during metamorphosis provide insight into the molecular modifications that directly reflect the dynamic developmental phenotype. Mass spectrometry metabolomics analysis of serum obtained from *Rana* [*Lithobates*] *catesbeiana* tadpoles at premetamorphic (functionally athyroid), prometamorphic (increasing TH), and metamorphic climax (peak TH) stages and from froglets showed significant changes in lipid metabolism pathways (Ichu et al., 2014). Triglycerides, the predominant components of anuran fat bodies (Sheridan and Kao, 1998), were significantly decreased at the froglet stage. Prior to metamorphic climax, however, classes of triglycerides were either present at steady levels or increased in abundance until metamorphic climax (Ichu et al., 2014). Nearly half of phosphatidylserine isomers detected were significantly decreased after metamorphic climax.

Arachidonic acid-derived eicosanoids, which function as signaling molecules, increased in abundance to metamorphic climax peak levels and then decreased at froglet stages. Dopamine also showed similar changes in abundance during metamorphic transitions. Collectively, these results suggest that lipid metabolites may have considerable roles in mediating signaling and structural changes that are critical for the coordination of post-embryonic anuran development across the whole organism (Ichu et al., 2014). The importance of lipophilic metabolites in coordinated whole-body metamorphic transitions was underscored by a multi-tissue analysis by matrix assisted laser desorption/Ionization-mass spectrometry imaging (MALDI-MSI) of premetamorphic *R. catesbeiana* tadpoles that were exposed to exogenous T_4 for 48 h (Luehr et al., 2018). Brain, notochord, eye, tail muscle, and to a lesser extent, liver, all exhibited changes in phosphatidylcholines, phosphatidylglycerols, phosphatidylinositols, phosphatidylserines and phosphatidylethanolamines. These variations in membrane-associated phospholipids reflected the changing physiology of these different organs that are a consequence of TH-dependent transcriptional cascades during metamorphosis (Luehr et al., 2018).

Given the sensitive and robust changes in lipid metabolites during metamorphosis, lipophilic molecules, particularly triglycerides, may be highly responsive to EDCs. Consequently, abnormal triglyceride abundance may serve as a useful biomarker for toxicological and environmental stress on intersecting TH- and lipid-dependent regulation (Gupta et al., 2008). The sensitivity of TH-dependent regulation is also underscored by the perturbation caused by sterol-like EDCs such as phytosterol. Analogous to cholesterol, phytosterols are released in high amounts in pulp mill effluents and can have deleterious effects on the biota within contaminated environments. Phytosterol exposure has been associated with decreasing T_3 plasma concentrations in female *Xenopus laevis* (Koponen et al., 2004). In fish, phytosterol effects are linked to affected sex steroid hormone biosynthesis and aberrant sexual characteristics (MacLatchy and Van Der Kraak, 1995). Lipophilic halogenated phenols, such as 2,4,6-triiodophenol can impair thyroid hormone activity in *X. laevis* tadpoles and bind non-specifically to lipoproteins in *Onchorhynchus mykiss* (rainbow trout) (Kudo and Yamauchi, 2005; Yamauchi and Sai, 2011).

Indeed, there are a vast array of lipophilic contaminants that can affect aquatic organisms in a TH-dependent manner that potentially intersects with metabolic regulatory pathways. A recent study of the organochlorine disaccharide sucralose demonstrated that it could affect the expression of TH-dependent metamorphic response genes (*thra*, *thrb*, *thibz*) in a manner reliant upon tissue specificity and T_4 status in *R. catesbeiana* premetamorphic tadpoles (Abbott and Helbing, 2021). Moreover, the abundance of transcripts associated with xenobiotic metabolism was modulated in response to sucralose exposure: cytochrome P450 3a4 (*cyp3a4*), constitutive androstane receptor (*nr1i3*) and pregnane X receptor (*nr1i2*) (Abbott and Helbing, 2021). Another comparable example is that of the anionic surfactant dioctyl sodium sulfosuccinate (DOSS), which has a surprisingly broad range of applications from food and personal products to industrial uses (Temkin et al., 2016). *R. catesbeiana* premetamorphic tadpoles exposed to T_3 or T_4 and DOSS had disrupted transcript abundance of TH-responsive genes (*thra*, *thrb* and *thibz*) in a tissue-specific manner (Corrie et al., 2021). DOSS has also been implicated as an obesogen as the male offspring of mouse dams orally administered DOSS during pregnancy developed increased fat masses in adulthood (Heindel, 2019; Temkin et al., 2019). These studies cumulatively show the exquisite life-stage sensitivity of TH-dependent signaling to xenobiotics and potential intersections with metabolic regulation.

In a study of chicken embryos exposed to the flame retardant hexabromocyclododecane (HBCDD), pipping success was significantly reduced (Crump et al., 2010). Gene expression associated with phase I and II metabolism, TH homeostasis, lipid regulation, and the GH/IGF axes were altered. Specifically, *IGF1* was decreased following *in ovo* exposure of chicken embryos to HBCDD; a similar response was observed in a companion study (Porter et al., 2014) in which five of the organic flame retardants examined reduced *Igf1* mRNA levels. Several of these cellular responses have been linked in mammals to PXR activation, highlighting the importance of receptor activation in mediating a response to environmental contaminants. The TH-responsive protein spot 14-a, a transcription factor associated with the regulation of adipogenic enzymes, is thought to play a role in TH stimulation of lipogenesis. Thyroid hormone-responsive protein spot 14-a mRNA levels were rapidly up-regulated by lipogenic stimuli including THs and a high carbohydrate diet in mice (LaFave et al., 2006).

The *in ovo* effects of two organophosphate flame retardants (TCPP and TDCPP) were investigated in chicken embryos, which showed that TCPP exposure increased the liver somatic index, delayed pipping time,

reduced tarsus length, and altered genes associated with xenobiotic metabolism, the HPT axis, and lipid metabolism (Farhat et al., 2013). TDCPP exposure further impaired embryo growth, gallbladder development, and plasma T_4 levels and affected the mRNA levels of phase I metabolizing enzymes.

Shen et al. (2019) assessed the effects of 2-ethylhexyl diphenyl phosphate (EHDPP) on cytotoxicity, mRNA expression and metabolism in a chicken embryonic hepatocyte assay (Shen et al., 2019). Two of the four genes that were associated with the TH pathway, *ttr* and TH-inducible hepatic protein (Thrsp), were down-regulated in a concentration-dependent manner following exposure to increasing concentrations of EHDPP (Shen et al., 2019). Thrsp is a crucial protein involved with TH-mediated lipogenesis and maintenance of triacylglycerol and medium-chain fatty acid levels (Yao et al., 2016).

Despite the importance of TH signaling in lipid metabolism and the potential for lipid feedback onto the HPT axis, this area of crosstalk has had comparatively little attention. Greater attention to obesogens and disruption through receptor-mediated pathways is needed. It is important to note that these receptor-mediated pathways do not require competitive binding with the receptor ligand binding domain, rather could be mediated indirectly through sequestration of transcriptional cofactors, by post-translational modification, or by epigenetic changes that change promoter recruitment to TH-responsive target genes. Indeed, such a mechanism has been observed for a related receptor, peroxisome proliferator-activated receptor gamma (PPARγ) (Egusquiza and Blumberg, 2020; Janesick and Blumberg, 2011).

6. Conclusions/final perspectives

The interaction between regulatory axes necessary to maintain homeostatic and stimulus-driven responses underscores the complexity of molecular functions required for organismal health and development and the plurality of deleterious effects that EDCs can elicit. The present review has illustrated that these are research areas that are primed for further investigation. Future research will need to address what are the common molecular targets that are the points of intersection between the HPT axis and any of the impinging axes including, but not limited to, the HPG, HPA and GH (Fig. 1). Identifying these central nodes of activity may likely reveal molecular fulcrums that mediate crosstalk between the different axes. Moreover, such molecular nodes may also be vulnerable targets to the activity of EDCs. Such an understanding would be invaluable for accounting for the mechanisms of action and the multiplicity of effects observed across different species, tissues, and developmental stages. The effects of EDCs on such hormonal axis crosstalk would extend beyond the molecular ramifications to cellular, physiological, behavioral, and whole-body consequences for exposed organisms. Indeed, the evidence suggests that factors that modulate endogenous signals due to reproductive status (androgens and estrogens), stress (glucocorticoids), dietary deficiencies (retinoids), or metabolic changes (lipids) may increase susceptibility to TH EDCs. Consequently, the present review addresses novel research questions to identify potentially vulnerable populations.

The comparatively more extensive studies conducted in mammalian models provides encouraging support for expanded investigation, and they highlight the paucity of data generated in other non-mammalian vertebrate classes (Fig. 2). Critical to such future studies will be the integration of large data approaches and high throughput methods to identify sensitive nodes between regulatory axes that are disrupted by EDCs. Combinatorial and sensitive cutting-edge approaches including, but not limited to, mass spectrometry analyses and variable sequencing techniques, in tandem with cellular and physiological assays will permit the successful interdisciplinary integration of genomics, transcriptomics, proteomics, metabolomics and epigenomics perspectives. Such types of broad analyses will permit a comprehensive assessment of the mechanisms of action for the "triad" of activity between the HPT and other hormonal axes and EDCs. The ensuing knowledge could readily be extended to the identification of potential biomarkers that could be systematically utilized in the expedient and informative assessment of environmental and organismal deleterious effects arising from abiotic and xenobiotic exposures. What is evident is that non-mammalian vertebrate classes, particularly birds and reptiles, have a notable dearth of research into this topic that limits our understanding of EDC action in the context of hormonal crosstalk.

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Funding

This work was supported by a Natural Sciences and Engineering Research Council (NSERC) Discovery grant RGPIN-2018-03816 to CCH and RGPIN-2020-06475 to VSL. VSL also holds a Canada Research Chair in Ecotoxicogenomics and Endocrine Disruption.

Research regarding animals or human subjects

This is a review of the published literature. No ethics approvals are needed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Tyler Jensen and Anna Dema for assistance in manuscript preparation. The authors are grateful to the Intersectoral Centre for Endocrine Disruptor Analysis (ICEDA)'s researcher network that facilitated this Special Issue.

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