Environment and endocrinology: The case of thyroidology

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Abstract

Evidence is accumulating for interference of selected endocrine disrupting chemicals (EDC) with the thyroid axis. EDC disturb thyroid hormone (TH) homeostasis leading to developmental defects, hypothyroidism and altered thyroid growth patterns. A rising incidence of papillary thyroid carcinoma (PTC) in several Western countries cannot be definitely accounted for by improved diagnosis or management of thyroid cancer or improved iodine supply. In recent studies, we and others detected, within the thyroid hormone axis, multiple molecular targets of disruption by EDC, which are used in cosmetics, as pesticides or plasticizers or consumed as plant-derived compounds with the diet or with nutritional supplements. Several of these agents exert adverse effects on thyroid growth and function in animal or in vitro cellular models. Major targets are the sodium iodide symporter (NIS), the hemoprotein thyroperoxidase (TPO), the T4 distributor protein transthyretin (TTR), the deiodinases, TH conjugating enzymes and the TR thyroid hormone receptor family. Still prevailing iodine deficiency in many parts of the world predisposes the thyroid gland to adverse effects of endocrine disrupters especially under phases of vulnerability during development and under adaptive challenges during diseases.

Keywords: Endocrine disrupter; Deiodinase; Transthyretin; Thyroperoxidase; Iodine; Thyroid; Hormone; Cancer; Goiter; Deficiency; Phytosteroid; Flavonoid; Isoflavonoid

1. Introduction

Among all environmental influences on the endocrine system, the effects of nutritional iodine deficiency, its impact on goitrogenesis and its consequences for fetal, neonatal and mental development have probably received the longest and still persisting interest. Iodine deficiency and its sequelae (cretininism, IQ deficits, hypothyroidism, goiter) still affect major parts (1.6 billion) of the world population not only in developing regions but also in highly industrialized countries and economies such as the European Union [1]. Though WHO had declared to eradicate iodine deficiency by the year 2000, this goal has not been reached. While adequate iodine intake has been reported even for some developing and industrial countries such as Bahrain, parts of South-Africa, Peru’s coastal region and Switzerland (> 100 to < 200 µg I/d), moderate to mild deficiency is known for Germany, New-Zealand, Australia, some parts of USA (> 50 to < 100 µg/d), also excess has been noticed in coastal Hokkaido (> 500 µg/d). These observations indicate ongoing requirement for worldwide iodine supplementation and enduring monitoring programmes. However, more economical, political, intellectual and financial resources are still dedicated to development, production, trade and annihilation of weapons in wars and to lethal warfare logistics than to prevention iodine deficiency, which is the single most important preventable cause of mental retardation worldwide and impaired child development.

Improvement of iodine supply has been practiced in many cultures and by physicians (J.R. Coindet, 1820) [1a] even before the element iodine had been discovered by F. Courtois and the thyroid glands main hormonal product had been identified as thyroxine (T4) by Kendall [2] in 1915 and chemically synthesized by Harington in 1927 [3].

Thyroid preparations had been systematically administered for treatment of hypothyroidism and myxedema since 1882 by MacKenzie, Bruns and Magnus-Levy [4].

Nevertheless, underlying iodine deficiency in the whole world population sets the stage for adverse reactions and effects of agents interfering at one or several steps and targets of the complex thyroid hormone. Stringent control of multiple and redundant feedback circuits allows efficient adaptation to alterations in iodine intake and metabolic challenges of thyroid hormone demand during development, growth, aging or states of healthiness or disease in adults.
2. Endocrine disrupters affect several targets of the thyroid hormone axis

In 2008, most of the relevant physiological, biochemical, cellular and molecular mechanisms and components of thyroid hormone (TH) biosynthesis, secretion, transport, cellular uptake, metabolism and action have been identified. Furthermore, the networks involved in the physiological feedback regulation of the thyroid hormone axis and its enormous capability of adaptation to altered nutritional, metabolic, physiological, pathological and pharmacological challenges are understood (Fig. 1, Table 1). This knowledge now enables us to also examine and partially understand in more detail mechanisms other than iodine deficiency or genetic makeup, which are involved in interference with the thyroid hormone axis. Apart from well-known pharmaceutical effects on the thyroid hormone axis, several nutritional, chemical and industrial environmental components affect one or more targets of this system [5]. Even additive, synergistic, but also antagonistic effects of these agents have been described. Table 2 summarizes some major reports on compounds known to target the thyroid hormone axis, their mechanism of action as far as it is known and species affected. Whether all of the interferences reported in wild life species or laboratory animals as well as in vitro cell culture or model studies also have relevance and impact for humans is still controversial. Several reasons have been listed, which might explain different outcome in animals versus humans such as different serum distributor proteins, which affect thyroid hormone pool size, tissue targeting and turnover. For example, the high affinity low capacity TH binding protein thyroxine binding globulin (TBG) is expressed only in higher mammals, most primates and humans, while transthyretin, the most conserved and most prevalent TH distribution protein is expressed and secreted mainly by the liver but also by the choroids plexus in species with a larger fat mass and brain size [6]. Other species rely on albumin as major TH binding protein and during development also fetal TH binding proteins are expressed. Depending on the pool size, biological half life and thyroid reservoir of TH and, at the same time, limited or adequate access to iodine supply nutritional, environmental, developmental of medical exposure to agents potentially disrupting the TH axis might have different impact, for example, in young or adult, slim or obese, male or female, pregnant or postmenopausal women or people living in equatorial, moderate or extremely cold climate zones [7], where different turnover and demand of TH are required to maintain and regulate body temperature, energy metabolism and thermogenesis [8].

Apart from strong data for EDC indicating goitrogenesis, interference with serum TH distributor proteins, which affects free and total TH concentrations, altered conjugation and elimination and impaired T3 formation by Dio, no convincing evidence has been presented for a role of these nutritional and environmental agents in thyroid carcinogenesis in humans. High-dose, long-term or experimental exposure of laboratory animals, mainly rats, indicate certain effects of some environmental or nutritional agents either during tumorigenesis, promotion, growth, invasion and/or metastasis at least under conditions of chronic iodine deficiency or with concomitant administration of other adverse agents [9–12].

3. Several classes of compounds affect thyroid hormone axis

During the recent years, in part funded by public domain research organizations, the European Union and other funds, several agents have been identified, which adversely affect synthesis, secretion, transport, metabolism and action of thyroid hormones. Among those are nutritional factors originating from water, soil, plants and animals, which enter life stock and human circulation unintentionally and inadvertently via the food chain. Other agents of synthetic origin might be contaminants of the food chain, cosmetics, objects of daily life use and our environment.

Among those agents are wide spread and abundant but also rare or only locally relevant compounds. Table 2 lists some major groups with known relevance for the thyroid axis.
Table 1
Interaction of endocrine disrupting compounds with key components of the thyroid hormone axis

<table>
<thead>
<tr>
<th>Component of thyroid hormone axis</th>
<th>Interfering agent</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>TRH</td>
<td>No reports</td>
</tr>
<tr>
<td>Pituitary</td>
<td>TRH receptor</td>
<td>No reports</td>
</tr>
<tr>
<td>Thyroid</td>
<td>TSH</td>
<td>Plant polyphenols [46–48]</td>
</tr>
<tr>
<td></td>
<td>TSHr</td>
<td>polyphenols [46–48]</td>
</tr>
<tr>
<td></td>
<td>NIS</td>
<td>perchlorate, nitrate, smoking [43,44,71]</td>
</tr>
<tr>
<td></td>
<td>Pendrin</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>Tg</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>TPO</td>
<td>soy products, BP2, F21388, bisphenol A [32,33,36]</td>
</tr>
<tr>
<td></td>
<td>Duox2</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>Dehal1</td>
<td>No reports</td>
</tr>
<tr>
<td>Distributor</td>
<td>TBG</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>pro-</td>
<td>Genistein, glycitein, daidzein, natural and synthetic (iso-) flavonoids [16,24,70,39,72–77]</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>Lipoproteins</td>
<td>No reports</td>
</tr>
<tr>
<td>Cellular uptake</td>
<td>MCT8</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>OATP14</td>
<td>No reports</td>
</tr>
<tr>
<td>Cellular metabolism</td>
<td>Dio1</td>
<td>natural and synthetic (iso-) flavonoids, OMC, MBC4 [5,12,16,70]</td>
</tr>
<tr>
<td></td>
<td>Dio2</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>Dio3</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>sulfotransferase</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>sulfatase</td>
<td>No reports</td>
</tr>
<tr>
<td></td>
<td>glucuronidyl transferase</td>
<td>No reports</td>
</tr>
<tr>
<td>Cellular action</td>
<td>TRα, TRβ</td>
<td>[72,73,78,79]</td>
</tr>
</tbody>
</table>

Limited information is available for direct interference of EDC with the hypothalamus or anterior pituitary components of the thyroid axis such as TRH, its receptor and TSH. However, by disruption of the TH negative feedback by EDC induced alterations in TH synthesis, metabolism and action elevated, decreased or unchanged serum TSH levels have been reported after exposure of laboratory animals to various EDC. A frequent observation is an inadequately normal, or decreased serum TSH, though elevated levels should be expected due to decreased serum T4 and/or T3 concentrations. Such constellations indicate an either normal intracellular T4 and T3, compensatory local increase of T3 by altered deiodinase activities, or even concomitant increase in systemic or local proinflammatory cytokine and growth factor levels, which might interrupt the negative feedback loop at the hypothalamic or pituitary level, there including the paracrine effects of folliculo-stellate cells [13–15].

Natural and synthetic polyphenols, flavonoids and isoflavonoids have been known for a long time to impair thyroid function. Especially soy products, including the isoflavone genistein, widely used even in concentrate extracts as phytosteroid with intended effects on sex steroid hormone receptor signaling in steroid hormone replacement therapy, are known as goitrogens inhibiting TPO, potent competitors for T4 and T3 binding to transthyretin and TH deiodination by deiodinases. These adverse effects may lead to goitrogenesis especially under conditions of inadequate iodine supply [16–23]. Whether such effects are relevant also for an iodine sufficient thyroid gland remains an open issue, especially for long-term administration. Especially children, pregnant and lactating women who have higher iodine turnover and demands might be at risk for goitrogenic effects of genistein, daidzein or their isoflavone or flavone congeners [24].

Table 2
Selected representative compounds affecting thyroid axis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Origin or occurrence</th>
<th>Target or effect on the thyroid axis</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutritional</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iso-) flavonoids, polyphenols</td>
<td>Plant dyes and components</td>
<td>TTR, deiodinases</td>
<td>[16,70]</td>
</tr>
<tr>
<td>Kojic acid</td>
<td>Malting rice byproduct</td>
<td>NIS</td>
<td>[9,10]</td>
</tr>
<tr>
<td><strong>Synthetic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perchlorate</td>
<td>Rocket fuel</td>
<td>NIS</td>
<td>[43,44,71]</td>
</tr>
<tr>
<td>PCB</td>
<td>Chemical industry</td>
<td>TTR</td>
<td>[72–75,39]</td>
</tr>
<tr>
<td>PBDE</td>
<td>Flame retardants</td>
<td>TTR</td>
<td>[76,77]</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>Plasticizer</td>
<td>TR, multiple</td>
<td>[12,63–68]</td>
</tr>
<tr>
<td>PAH</td>
<td>Combustion processes</td>
<td>UDP-glucuronoytransferase</td>
<td>[12]</td>
</tr>
<tr>
<td>UV screens</td>
<td>Cosmetics, daily life household products</td>
<td>TPO, NIS</td>
<td>[32,33,69]</td>
</tr>
<tr>
<td><strong>Pesticides</strong></td>
<td>Ubiquitous</td>
<td>TR &amp; Transcription</td>
<td>[78,79]</td>
</tr>
</tbody>
</table>
Cruciferous plants, such as cabbage, Brussels sprouts, legumes and cassava, especially, if inadequately processed due to lack of energy resources, contain goitrogenous substances that either interfere with iodine uptake by NIS, iodide organization by TPO or other reactions of the TH axis. These adverse actions can be prevented or partially ameliorated by improving iodine intake by diversified diet. As iodine content of natural food and water depends primarily on the supply of iodine in the soil, consequent use of iodized salt or comparably effective strategies for iodination campaigns in many regions of our planet remain a permanent challenge to balance or counteract nutritional and environmental exposure to agents interfering with the thyroid hormone axis. The normal human thyroid can handle exposure to excess iodide supply via the Wolff-Chaikoff effect, which prevents further iodide uptake by downregulation of NIS expression and functional integration into the basolateral plasma membrane. Therefore, also long-term intake of iodized salt is considered safe. In rare cases iodine induced goiter, hypothyroidism or hyperthyroidism have been observed, probably on a background of higher genetic susceptibility or in association with other diseases.

Nutrient- or fermentation-derived soy metabolites (e.g., kojic acid, also used for skin bleaching in Japan and some developing countries) lead to thyroid dysfunction including neoplasia if applied to rodents for extended periods at higher concentrations [25,26].

Using F21388, a synthetic flavonoid, inhibition of type 1 5′-deiodinase (5′DI), displacement of T4 from the TH distributor protein transthyretin and altered TH secretion and metabolism was shown in rats [27–30]. Apart from Genistein, a soy isoflavone, also xanthohumol, a hop polyphenol, competes with T4 for TTR binding [16]. F49209, another synthetic flavonoid, crosses the rat placenta and may affect T4 availability in the fetal rat brain [31]. In the rat model, altered expression and activity of the TH-regulated endpoints malic enzyme and 5′DI in the liver and the kidney and changes in pituitary TSH α and β and in 5′DI mRNA levels were observed after acute or chronic administration of various EDC [32–38]. TPO, NIS, 5′DI and TSH receptor mRNA levels were altered in the rat thyroid. In vitro, the UV screen benzophenone 2 (BP2) in combination with H2O2 inactivated TPO, an effect that was prevented by adequate or excess iodide. Another UV screen, 4-methylbenzylidene-camphor (4-MBC), inhibited iodide uptake by NIS in FRTL-5 rat thyroid cells.

In vivo, in rats, these two UV screens (BP2, 4-MBC) caused decreased serum levels of T4 and T3, while TSH and thyroid weight were increased, classical indicators of hypothyroidism [35]. Thus, by interfering with thyroid hormone synthesis, BP2 and 4-MBC increased TSH serum levels and triggered an abnormal growth stimulus for the thyroid resulting in goitrogenesis.

As all of these reactions represent essential steps in TH biosynthesis, this data suggests complex interference of EDC with the thyroid axis affecting both individual endpoints and hormonal feedback regulation. While for some EDC, compensatory or adaptive mechanisms may have ensured a still normal thyroid growth, they appear inadequate in other cases, especially 4-MBC and BP2, resulting in goiter and thus possibly providing a basis for thyroid neoplasia.

Exposition to polybrominated diphenyl ethers (PBDE) or polychlorinated biphenyls (PCB) during work or in our environment may also cause hypothyroidism [39]. Polychlorinated biphenyls are effective as thyroid tumor promoters in rats after initiation by diisopropanol-nitrosamine [40]. As several EDC exhibit estrogenic potency they might contribute to thyroid carcinogenesis similar to estradiol [40a]. This effect might provide a link to observations on female preponderance of benign and malignant thyroid dysfunctions (autoimmune diseases M. Hashimoto and M. Basedow, thyroid nodules and cancer), which remains to be analysed.

Recently, the potentially harmful effects of perchlorate exposure by drinking water for thyroid function received major attention in the scientific and public discussion. Perchlorate is a potent and even diagnostically used inhibitor of iodide uptake catalyzed by NIS, which is located in the basolateral thyrocyte membrane [41]. Perchlorate is one of the major rocket fuels and several areas around civilian or military rocket-related sites and their draining rivers are contaminated by perchlorate, easily soluble in water. Whether this exposure leads to goitrogenesis or other forms of thyroid dysfunction needs to be considered and examined in more detail and extent [42–45].

While NIS and TPO seem to be the major EDC targets in thyroid hormone biosynthesis, thyroglobulin, dual function oxidase 2 and cathepsins involved in hydrolysis of iodinated Tg are not affected by EDC. In contrast, TSH receptor, the key regulator of thyrocyte function and its subsequent signal transduction are affected by some EDC such as polyphenols, (iso-)flavonoids and a few other compounds [46–50]. Whether these effects are the basis of therapeutic effects exerted by some plant extracts used in traditional folk remedies has not been finally proven.

4. The serum TH distributor protein transthyretin is a major target for several EDC

Strong effects of many EDC are exerted on the serum thyroid hormone distributor protein transthyretin. While TH binding to the high affinity binding protein TBG and the high capacity low affinity binding protein albumin are not affected by EDC, the TH binding site of transthyretin is a rather specific target of several classes of EDC such as (iso-)flavonoids, PCB, PBDE and others. The molecular basis of this rather selective interaction of EDC with the TH binding site of transthyretin remains unclear, because other TH binding sites such as TBG, albumin, TR are unaffected. Among all EDC, the highest affinity for transthyretin has been described for genistein, which is equipotent to T4 in binding and also the natural flavonoid luteolin of the synthetic derivative F21388 show avid and selective transthyretin binding [24]. T4 (and T3) are displaced and shifted to albumin (or TBG if present in the respective species). The result of this competition is a transient increase in free TH concentrations, altered tissue uptake and elimination. Long-term exposure to these compounds might result in loss of circulating TH by the urine or feces and if not compensated by enhanced thyroid hormone synthesis and secretion result in goitrogenesis. This
also requires adequate iodide intake to account for the enhanced (renal) elimination of intact TH. Along these lines of reasoning EDC, especially (iso-)flavones chronically consumed in high extract doses might impose a significant risk to develop goiter, especially if inadequate iodine is not warranted. EDC induced goiters (isoflavone goiters) thus might be a major risk factor for women on long-term high-dose phytosteroid-based hormone replacement therapy. Apart from (peri- and postmenopausal) women, babies and young children might be another risk group, as their thyroidal iodine and iodinated Tg stores are rather limited in contrast to adults living in areas with adequate iodine supply, whose stored iodinated Tg would last for up to three months of necessary TH release without de novo synthesis.

5. Cellular uptake, metabolism and action of TH is affected by EDC

Not much is known whether EDC affect TH uptake into cells, which is enabled by the recently discovered TH transporters MCT8 and OATP14 and other permeases. More detailed data and systematic structure activity relationships have been reported for EDC interaction with the intracellular TH deiodinases and conjugating enzymes. Here, especially Dio1 is strongly inhibited by EDC from different categories (see tables). In general trend, both Dio2 and Dio3 are less potently affected by EDC than Dio1. Based on these considerations the major target sites for generation of circulating T3, catalyzed by hepatic, renal and thyroid Dio1, are candidates for EDC inhibition, while the T3 forming Dio2 and the TH inactivating Dio2 might be less efficiently affected. Apart from Dio reactions several EDC also inhibit TH conjugating enzymes such as sulftotransferase, glucuronidase and sulfatases. Interference with TH conjugation is known for many PCB, PBDE and related compounds [51–54], which under chronic exposure lead to an altered relation between circulating serum TH and TSH, thus altering both the pituitary setpoint of the negative feedback regulation and at the same time increasing TH elimination, again a situation requiring adequate iodine supply for compensatorily increased TH synthesis and secretion. For several of the ED effects on TH glucuronidation and thus, elimination have been described [55–58]. Induction of conjugating enzymes such as sulftotransferases might involve the xenobiotic receptor constitutive androstane receptor (CAR, NR1I3), which acts as chemosensor and its activation leads to decreased serumT4 and T3 levels and elevated TSH.

More detailed information on interference of ED has been accumulated for inhibition of Dio1 and thus, T3 production. Several classes of ED are potent Dio1 inhibitors, e.g. (iso-)flavonoids, polyphenols, aromatic and polycyclic phenolic ring systems. Many of these agents act as competitive inhibitors and their \( K_i \) values reach equimolar ranges to the \( K_m \) of T4 or rT3 [59–61,32,34]. Apparently the Dio1 active site not only accommodates several iodothyronines substrates (e.g., T4, rT3, T3-sulfate) but also various ED acting as competitors of TH in this reaction. Whether this inhibition of TH deiodination exerts major effects on TH homeostasis, T3 formation and feedback regulation of the thyroid axis remains to characterized in more detail. While inhibition of in vitro deiodination of TH by various ED in membrane preparations or cell culture models is quite effective, administration of these agents in vivo not necessarily impairs T3 formation and TH homeostasis. Several reasons account for this observation. Inhibition of Dio1 activity can be compensated by Dio2 action or reduced activity of Dio3, constellations which would maintain circulating serum T3 levels. In addition, several of the ED which are potent in vitro Dio1 inhibitors also show high binding and competition with the TH binding to transthyretin. This would lead to limitations of cellular uptake and availability of ED to intracellular Dio1 and impaired inhibitory potency. Such scenarios have been demonstrated for the synthetic flavonoid F21388, which is an avid ligand for transthyretin but apparently dose not reach sufficiently high intracellular concentrations for effective Dio1 inhibition [27–30,62]. Apparently, the network of thyroid hormone homeostasis exhibits several redundant or compensatory fail-safe mechanisms required for maintenance and adaptation of adequate circulating serum and tissue T3 levels, which are required for control and maintenance of T3-dependent energy and intermediary metabolism.

Considering the interference of ED with the serum thyroid hormone distributor protein transthyretin and intracellular deiodinases, their potential interference with the T3 receptors could by a further target. However, only few of the ED were shown to significantly compete with T3 binding to TRs, while interference at the prereceptor control levels of ligand availability to TRs is quite obvious. TR-binding has been demonstrated, for example, for bisphenol A in several in vitro and in vivo models [63–68,12]. As bisphenol A also strongly interferes in the sex steroid signaling pathways, cause-effect relationships are quite difficult to establish. Nevertheless, the decision of a toxicology panel of the National Toxicology Program, U.S. Department Of Health And Human Services (http://cerhr.niehs.nih.gov) which obviously lacked endocrine expertise in the report on Developmental Toxicity of Bisphenol A to declare bisphenol A as not relevant with respect to disruption of the thyroid hormone axis is difficult to reconcile with published scientific data and met with major surprise in the concerned scientific community. Obviously, more and especially also, interdisciplinary research is needed to adequately address issues of endocrine disruption in general and especially during development.

Especially, agents such as several pesticides, the plasticizer bisphenol A, the UV screens 4-MBC or Octylmethoxycinnamate (OMC), which is worldwide one of the most frequently used chemical UV-filters in sunscreens to protect the skin against the noxious influence of UV radiation and several other ED agents need to be examined in more detail with respect to their mechanism of action in the endocrine and especially the thyroid hormone system, their distribution and exposure levels, environmental persistence or accumulation in the food chain [32,36,5,69].

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