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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 (cretinism, 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.

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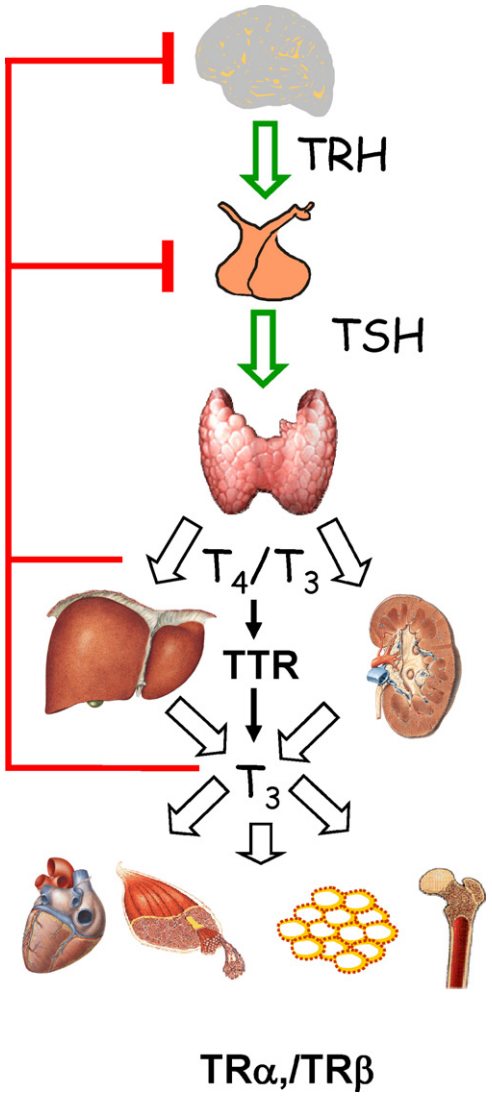

Fig. 1. Targets for environmental modulation of the thyroid hormone axis. TRH: thyroliberin; TSH: thyrotropin; T4: L-Thyroxine; T3: 3,3′,5-Triiodo-L-thyronine; TTR; transthyretin, TR: T3-receptor.

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 inadvertedly 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.