Environmental Research 135 (2014) 361–375

Contents lists available at ScienceDirect

Environmental Research

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

Review

Deiodinases and thyroid metabolism disruption in teleost fish

Sergio Jarque [a,*], Benjamin Piña [b]

[a] Masaryk University, Faculty of Science, RECETOX, Kamenice 5/753, CZ62500 Brno, Czech Republic
[b] Institute of Environmental Assessment and Water Research, IDAEA-CSIC, Jordi Girona, 18, 08034 Barcelona, Spain

ARTICLE INFO

Article history:
Received 18 July 2014
Received in revised form
9 September 2014
Accepted 26 September 2014

Keywords:
Iodothyronine deiodinases
Thyroid disruption
Physical factors
Environmental pollutants
Teleosts

ABSTRACT

Many xenobiotic compounds with endocrine disrupting activity have been described since the late eighties. These compounds are able to interact with natural hormone systems and potentially induce deleterious effects in wildlife, notably piscine species. However, while the characterization of endocrine disruptors with "dioxin-like", estrogenic or androgenic activities is relatively well established, little is known about environmentally relevant pollutants that may act at thyroid system level. Iodothyronine deiodinases, the key enzymes in the activation and inactivation of thyroid hormones, have been suggested as suitable biomarkers for thyroid metabolism disruption. The present article reviews the biotic and abiotic factors that are able to modulate deiodinases in teleosts, a representative model organism for vertebrates. Data show that deiodinases are highly sensitive to several physiological and physical variables, so they should be taken into account to establish natural basal deiodination patterns to further understand responses under chemical exposure. Among xenobiotic compounds, brominated flame retardants are postulated as chemicals of major concern because of their similar structure shared with thyroid hormones. More ambiguous results are shown for the rest of compounds, i.e. polychlorinated biphenyls, perfluorinated chemicals, pesticides, metals and synthetic drugs, in part due to the limited information available. The different mechanisms of action still remain unknown for most of those compounds, although several hypothesis based on observed effects are discussed. Future tasks are also suggested with the aim of moving forward in the full characterization of chemical compounds with thyroid disrupting activity.

1. Introduction

The number of substances related to human activities that can cause harmful effects on organisms and ecosystems is increasing. Among all these potentially hazardous compounds, the so-called endocrine disrupting chemicals (EDCs), i.e. exogenous substances or mixtures that alter function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002), merit special attention. These compounds are extremely heterogeneous and, apart from being found as natural molecules like pheromones or phytoestrogens, are produced as synthetic products in pharmaceutical drugs, pesticides, electrical components, plastics and so on. Some EDCs are hydrophilic and rapidly degraded or metabolized, while some others are typically semi-volatile, lipophilic and resistant to environmental degradation by biological, chemical and photolytic reactions, which facilitates persistence, long-range transportation, bioaccumulation and biomagnification through food chain (Fernández et al., 2003; Van Drooge et al., 2004; Wang et al., 2009). As result, EDCs are virtually now widespread in the environment.

Adverse effects associated to EDCs have been documented in many organisms since the late eighties (Colborn et al., 1993; Tyler et al., 1998), so there is a growing interest in the characterization and the understanding of their modes of action. However, while this task is relatively advanced with respect to the compounds with "dioxin-like", estrogenic or androgenic activities, much less is known about environmentally relevant pollutants that may act at thyroid system level. In fish, thyroid metabolism plays a pivotal role in some development processes such as growth and

Abbreviations: ; BTBPE, 1,2-bis(2,4,6-tribromophenoxy)ethane; EDC, endocrine disrupting chemicals; HBCD, hexabromocyclododecane; HPT, hypothalamus–pituitary–thyroid; ID, ID1, ID2, ID3, iodothyronine deiodinase, type 1, type 2, type 3; mono, monodeiodination; OH-PBDE, hydroxilated PBDE; PAH, polycyclic aromatic hydrocarbon; PBDE, polybrominated difenyl eter; PCB, polychlorinated biphenyls; PFC, perfluorinated chemical; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PXR, pregnane X receptor; reverse-T3, (rT3); T2, 3,3′-diiodothyronine; T3, 3,5,3′-triiodothyronine; T3IRD, T3 inner ring deiodination; T3ORD, T3 outer ring deiodination; T4, thyroxine; T4IRD, T4 inner ring deiodination; T4ORD, T4 outer ring deiodination; TH, thyroid hormone; TR, thyroid receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulant hormone

* Corresponding author.
E-mail addresses: jarque@recetox.muni.cz (S. Jarque), benjami.pina@idaea.csic.es (B. Piña).

http://dx.doi.org/10.1016/j.envres.2014.09.022
0013-9351/

maturation (Sower et al., 1985; Walpita et al., 2009), smoltification (Björnsson et al., 2011), osmoregulation (Peter, 2011) and larval metamorphosis (Klaren et al., 2008; Taillebois et al., 2011). Additionally, the thyroid system is involved in immune system development (Lam et al., 2005), regulation of the intermediate metabolism (Kao et al., 1999) and behavior patterns (Edeline et al., 2005; Imbert et al., 2008). Therefore, alterations in the thyroid metabolism may affect those processes, leading to physiological abnormalities and other adverse effects, which in turn may compromise the correct balance of populations and even species survival.

Teleosts is a fish group broadly used as environmental indicator and cost-effective representative model in vertebrate growth and development owing to the relatively high degree of conservation between hormone regulations among the different species (McRobb et al., 2014; Jarque et al., 2010; Scholz and Mayer, 2008; Quirós et al., 2007). The use of these models for thyroid disruption is still incipient, but steadily growing, both in laboratory studies (Corcoran et al., 2012; Pelayo et al., 2012; Thienpont et al., 2011) and in natural populations' surveys (Jarque et al., 2014; Schnitzler et al., 2012; Picard-Aitken et al., 2007). Brown et al. (2004a) reviewed the potential contaminants that may impact the thyroid system in teleost fish. Some previous studies suggest that most of these compounds may not directly interact with thyroid receptors (TRs) (Crofton, 2008; Suvorov et al., 2011), but rather affect additional elements within the thyroid signaling pathway. Iodothyronine deiodinases (IDs) have been suggested as potential biomarkers for thyroid disruption because of their essential function in controlling thyroid homeostasis (Orozco and Valverde-R, 2005). However, the use of IDs activity or expression levels as thyroid disruption markers is still under debate since there are no specific patterns associated to chemical exposure. In the present review we intend to bring new knowledge by analyzing IDs behavior, not only under chemical exposure, but also under the influence of several natural factors (basal response), according to data published so far. This information allows us to consequently point to several directions where to emphasize future research. Also, by establishing common patterns associated to particular families of compounds, the suitability of using IDs as thyroid biomarkers may be evaluated.

2. The role of deiodinases in the thyroid system of fish

Thyroid metabolism is under control of the hypothalamus–pituitary–thyroid axis (HPT), which constitutes a multi-loop feedback mechanism present in all higher vertebrates where the thyroid gland is responsible for the synthesis of thyroid hormone (TH), the major regulatory factor (Fig. 1). Unlike terrestrial vertebrates, thyroid glands from teleosts do not present a typical glandular structure, but forming a number of follicles with variable diameters depending on species and functional glandular stage. The follicular hormone synthesis is regulated by thyrotropin, also known as thyroid stimulant hormone (TSH), which is released by the pituitary in response to increases of thyrotropin-releasing hormone (TRH) from the hypothalamus (MacKenzie et al., 2009). TH is firstly synthesized as prohormone thyroxine (T4) to be conversed later to active hormone, i.e. 3,5,3′-triiodothyronine (T3), or inactive metabolites, i.e. reverse-T3 (rT3) and 3,3′-diiodothyronine (T2). Conversion between forms is possible by enzymatic action of the IDs, a group of three transmembrane selenoproteins that selectively remove iodine moieties in the in-/activation reactions; type 1 iodothyroninedeiodinase (ID1) and type 2 iodothyroninedeiodinase (ID2) activate T4 to T3 by outer ring deiodination (ORD); type 3 iodothyroninedeiodinase (ID3) catalyses inner ring deiodination (IRD) and generates the inactive metabolites rT3 or T2 from T4 and T3, respectively (Fig. 2).

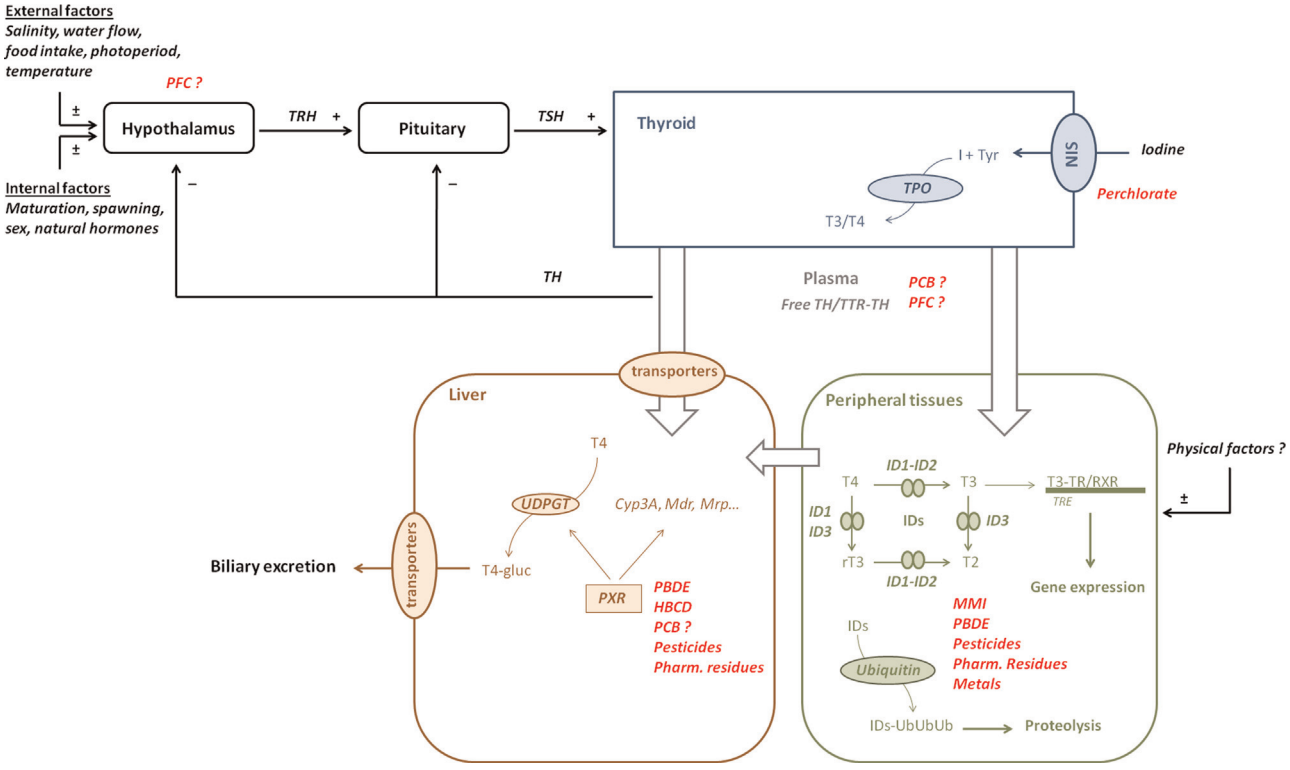

Fig. 1. Most relevant elements in the hypothalamus-pituitary-thyroidhypothalamus–pituitary–thyroid axis. Hypothetical sites of interaction for physical factors (black) and chemical compounds (red) are indicatedindicated for each physiological compartment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)