Biochimica et Biophysica Acta 1830 (2013) 3956–3964

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

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

Review

Role of the type 2 iodothyronine deiodinase (D2) in the control of thyroid hormone signaling☆

Rafael Arrojo e Drigo [a], Tatiana L. Fonseca [a], Joao Pedro Saar Werneck-de-Castro [a,b,c], Antonio C. Bianco [a,*]

[a] Division of Endocrinology, Diabetes and Metabolism, University of Miami, Miller School of Medicine, Miami, FL, USA
[b] Instituto de Biofisica Carlos Chagas, Brazil
[c] Escola de Educacao Física e Desportos, Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 5 June 2012
Received in revised form 11 August 2012
Accepted 23 August 2012
Available online 29 August 2012

Keywords:
Thyroid hormone
Deiodinase
Metabolism
Selenoprotein

ABSTRACT

Background: Thyroid hormone signaling is critical for development, growth and metabolic control in vertebrates. Although serum concentration of thyroid hormone is remarkable stable, deiodinases modulate thyroid hormone signaling on a time- and cell-specific fashion by controlling the activation and inactivation of thyroid hormone.
Scope of the review: This review covers the recent advances in D2 biology, a member of the iodothyronine deiodinase family, thioredoxin fold-containing selenoenzymes that modify thyroid hormone signaling in a time- and cell-specific manner.
Major conclusions: D2-catalyzed T3 production increases thyroid hormone signaling whereas blocking D2 activity or disruption of the Dio2 gene leads to a state of localized hypothyroidism. D2 expression is regulated by different developmental, metabolic or environmental cues such as the hedgehog pathway, the adrenergic- and the TGR5-activated cAMP pathway, by xenobiotic molecules such as flavonols and by stress in the endoplasmic reticulum, which specifically reduces de novo synthesis of D2 via an eIF2a-mediated mechanism. Thus, D2 plays a central role in important physiological processes such as determining T3 content in developing tissues and in the adult brain, and promoting adaptive thermogenesis in brown adipose tissue. Notably, D2 is critical in the T4-mediated negative feed-back at the pituitary and hypothalamic levels, whereby T4 inhibits TSH and TRH expression, respectively. Notably, ubiquitination is a major step in the control of D2 activity, whereby T4 binding to and/or T4 catalysis triggers D2 inactivation by ubiquitination that is mediated by the E3 ubiquitin ligases WSB-1 and/or TEB4. Ubiquitinated D2 can be either targeted to proteasomal degradation or reactivated by deubiquitination, a process that is mediated by the deubiquitinases USP20/33 and is important in adaptive thermogenesis.
General significance: Here we review the recent advances in the understanding of D2 biology focusing on the mechanisms that regulate its expression and their biological significance in metabolically relevant tissues. This article is part of a Special Issue entitled Thyroid hormone signalling.
© 2012 Elsevier B.V. All rights reserved.

1. Introduction

It has been 60 years since the identification of the 3,5,3′-triiodothyronine (T3) molecule in human plasma [1]. Today, it is well accepted that T3 is the biologically active thyroid hormone that initiates its signaling by interacting with thyroid hormone receptors (TR), ligand-dependent transcription factors that control the expression of T3-dependent genes. The historical view was that circulating T3 diffuses into cells and gains access to the nucleus, hence interacting with TRs. Today it is recognized that circulating thyroid hormone levels hardly ever fluctuate, remaining fairly constant during the entire adult life of healthy individuals [2]. Therefore, it is fair to ask "how can thyroid hormone signaling initiate or terminate important biological processes if not through changes in plasma levels?" The answer is deiodination.

The modern paradigm of thyroid hormone action recognizes that T3 and thyroxine (T4) enter target cells through specific thyroid hormone transporters [3], are metabolized through thioredoxin fold-containing selenoenzymes, the deiodinases, and finally diffuse into the cell nucleus. Deiodination either activates T4 to T3 (type I (D1) and type II (D2) deiodinases) or irreversibly inactivates T3 to T2 and T4 to rT3 (D1 and the type III deiodinase, D3). The net amount of T3 eventually occupying the TR defines the thyroid hormone transcriptional footprint in each cell type and is strongly influenced by the activity of the deiodinases [4]. Thus, by differentially expressing D2 or D3, T3-target cells do play an active role in customizing thyroid hormone signaling, a mechanism that is tissue-specific and not at all apparent by simply studying circulating levels of thyroid hormone.

☆ This article is part of a Special Issue entitled Thyroid hormone signalling.

* Corresponding author at: 1400 NW 10th Avenue, Suite 816, Miami, FL, 33136, P.O. Box 016960 (D-56), USA.
E-mail address: abianco@deiodinase.org (A.C. Bianco).

0304-4165/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbagen.2012.08.019

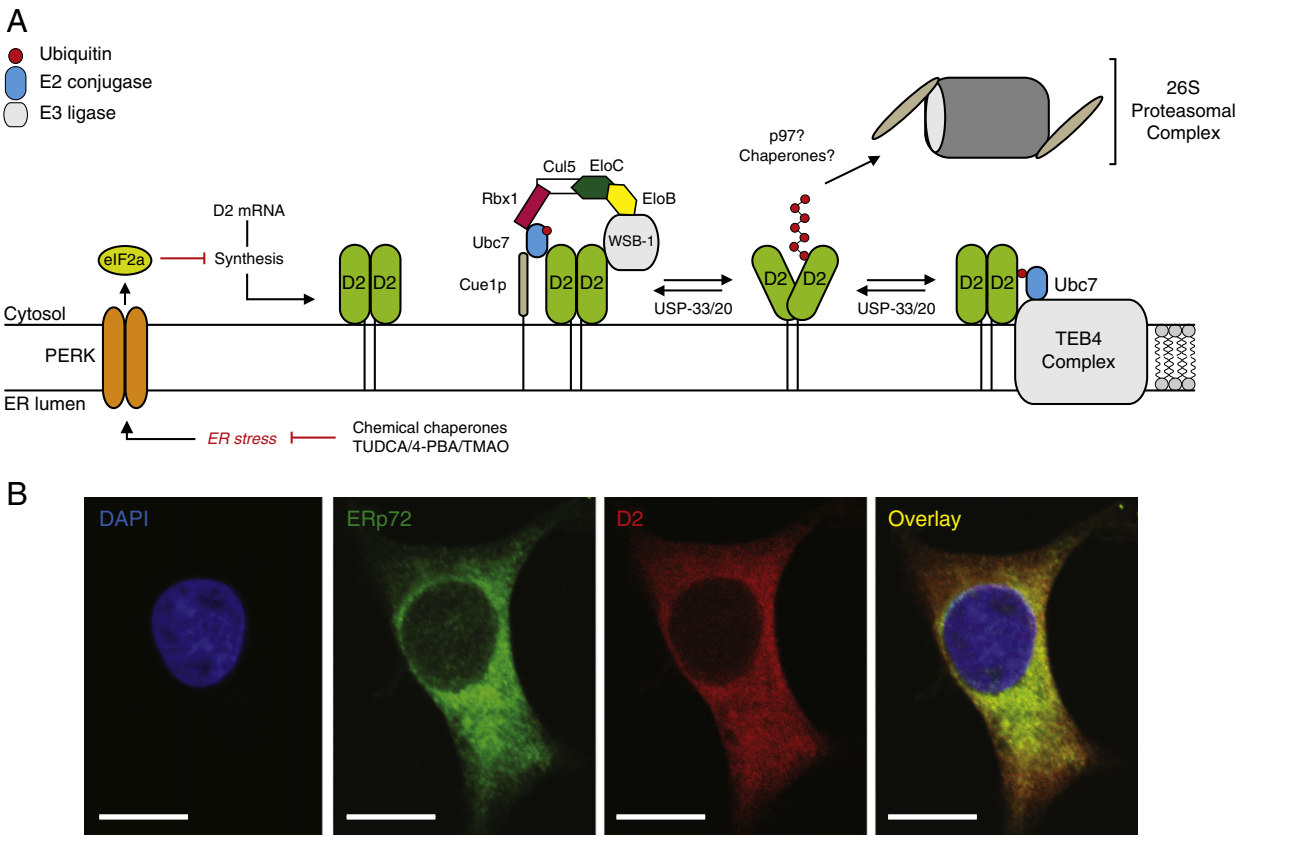

Fig. 1. D2 is regulated at the post-transcriptional level. The short-lived dimeric enzyme type 2 iodothyronine deiodinase (D2) is an endoplasmic reticulum (ER) resident protein regulated by the ubiquitin–proteasome pathway. (A) D2 ubiquitination is triggered by substrate (T4 or rT3) binding to D2's catalytic core, when two different E3 ubiquitin ligases, WSB-1 and TEB4, play key roles in regulating cellular D2 levels. Ubiquitinated D2 complexes (Ub-D2) are catalytically inactive and can either be de-ubiquitinated by the action of the deubiquitinates (DUBs) USP20 and USP30, rescuing D2 activity; or are directed to the 26S proteasomal complex for terminal degradation. Besides ubiquitination, cellular D2 levels are regulated at the translational level by the ER stress pathway, which blocks D2 protein synthesis upon disruption of ER homeostasis and activation of the PERK–eIF2a pathway. Conversely, ER stress can be attenuated or even reversed by treatment of cells with chemical chaperones, thus lifting the negative effect of ER stress on D2 synthesis and finally increasing D2 activity. Modified from [6]. In (B), immunocytochemistry staining and confocal imaging of HEK-293 cells stably expressing a YFP-D2 construct. From left to right: nuclei (DAPI, blue); ERp72, an ER marker (green); and D2 (red). The overlay of all signals (yellow) is shown on the last picture on the right. Scale bar, 12 μm.

A better understanding of deiodinase structure was achieved through hydrophobic cluster analysis (HCA), a computer-based molecular modeling that revealed a high degree of homology (~50%) among the three deiodinases. All are dimeric type I integral membrane proteins anchored through a single transmembrane domain located in the amino terminus [5]. Whereas D1 is a plasma membrane-resident protein, D2 resides in the endoplasmic reticulum (ER) [6] (Fig. 1). In contrast, D3 distributes to the plasma membrane or the nuclear membrane depending on the oxygen availability [7–9]. Whereas under normoxic conditions D3 is sorted to the plasma membrane, ischemia or hypoxia rapidly redirects D3 from the ER to the nuclear envelope via a HSP40-mediated shuttle mechanism, where it inactivates T3 [8].

2. Mechanisms controlling D2-mediated T3 production

D2 is under transcriptional and post-transcriptional control (Table 1) that is triggered by different developmental, metabolic or environmental

Table 1
Regulatory pathways of D2.

Tissue	Stimuli	Mechanism	Pathway/factor
BAT	Bile acids	Transcriptional	TGR5–cAMP [13]
	Chemical chaperones	Transcriptional	Unknown [38]
	Cold exposure	Transcriptional	β-Adrenergic receptor-cAMP [4,85]
		Post-transcriptional	Deubiquitination — USP33 [27]
Bone (*tibia growth plate*)	Indian hedgehog (Ihh)	Post-transcriptional	Ubiquitination — WSB1 [22]
Brain	LPS	Transcriptional	NF-kappaB [75]
	Thyroxine (T4)	Post-transcriptional	Ubiquitination [6,14] — TEB4 [25], WSB-1 [22]
Lung (*airway cells*)	LPS	Transcriptional	Injury [35,36]
	ER stress	Post-transcriptional	PERK-eIF2a [15]
	Chemical chaperones	Post-transcriptional	Reversal of ER stress [15]
Skeletal muscle	Bile acids	Transcriptional	TGR5–cAMP [13]
	Kaempferol (KPF)	Transcriptional	cAMP [41]
	Forskolin (FSK)	Transcriptional	cAMP [98]
	Cold exposure	Transcriptional	Adrenergic receptors [103]

The table describes the regulatory pathways and factors that affect D2 expression levels.

Download English Version:

https://daneshyari.com/en/article/10800609

Download Persian Version:

https://daneshyari.com/article/10800609

Daneshyari.com