Available online at www.sciencedirect.com
ScienceDirect
Maturitas 55S (2006) S14–S25
MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL
www.elsevier.com/locate/maturitas

Effects of isoflavonoids and other plant-derived compounds on the hypothalamus–pituitary–thyroid hormone axis

Inka Hamann [a,*], D. Seidlova-Wuttke [b], W. Wuttke [b], J. Köhrle [a]

[a] *Institut für Experimentelle Endokrinologie und Endokrinologisches Forschungszentrum, Charité, Universitätsmedizin Berlin, Charitéplatz 1, D-10117 Berlin, Germany*
[b] *Department of Clinical and Experimental Endocrinology, University of Goettingen, Robert-Koch-Str. 40, D-37075 Goettingen, Germany*

Abstract

Objectives: There is increasing concern that exposure to flavonoids may lead to endocrine disruption of the hypothalamus–pituitary–thyroid hormone axis, and, additionally, there is evidence that secondary plant metabolites contained in our daily diet or used for hormone-replacement therapy act as hormones themselves, similar to known isoflavonoid effects in the steroid hormone network. These compounds of natural origin affect the thyroid hormone feedback system by interference with different components of this homeostatically regulated system: biosynthesis, secretion and metabolism, transport, distribution, and action of thyroid hormones including the feedback mechanism. Genistein and daidzein, the major components of soy, influence thyroid hormone synthesis by inhibition of the iodide oxidizing enzyme thyroperoxidase, interfere with thyroid hormone transport proteins and 5′-deiodinase type I activities in peripheral tissues, which leads to altered thyroid hormone action at the cellular level. Synthetic flavonoids, such as F21388, structurally similar to thyroxine, cross the placenta and reach the fetal brain of animal models also.
Methods: A review of effects of various isoflavonoids and plant-derived extracts on the hypothalamus–pituitary–thyroid axis is the major objective of this contribution. In addition, new experimental data obtained in ovariectomized (ovx) rats will be presented. The substances tested here were plant extracts of *Agnus castus*, *Belamcanda chinensis*, *Silybum marianum*, *Cimicifuga racemosa*, and a commercially available soy product.
Results: In ovx rats the extract at two doses showed no effects on circulating TSH and thyroid hormone serum levels after 3 months of treatment.
Conclusion: The thyroid hormone network has a considerable capacity to compensate for disturbances of this feedback system as it is necessary for various metabolic and catabolic reactions and development. With respect to still insufficient nutritive iodine-supply of almost one third of the world population, possible adverse flavonoid actions on the thyroid hormone axis have to be examined more closely.

Keywords: Isoflavonoid; Secondary plant metabolites; Soy; Genistein; *Cimicifuga racemosa*; Thyroid hormone; Thyroperoxidase; Transthyretin; 5′-Deiodinase

* Corresponding author. Tel.: +49 30 450 576097; fax: +49 30 450 524922.
E-mail address: inka.hamann@charite.de (I. Hamann).

0378-5122/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2006.06.013

1. Introduction

Thyroid hormones are synthesized, stored and secreted by the thyroid gland under control of the hypothalamus–pituitary–periphery–feedback system dependent on the supply of two essential trace elements—iodine and selenium [1]. The main stimulator of thyroid hormone synthesis is thyroid-stimulating hormone (TSH), secreted from the anterior pituitary—it enhances all processes necessary for thyroid hormone biosynthesis: protein biosynthesis, organification of intra-thyroidal iodide, and stimulation of thyroglobulin (Tg) release.

The thyroid gland concentrates iodide from the circulation against a gradient into the follicles via the sodium-iodide symporter (NIS) that is located in the basolateral plasma membrane of the thyrocytes, the gland's functional units. The apical iodide channel pendrin then mediates the chloride uptake from the lumen and iodide efflux to the apical colloid space of the thyrocytes [2,3]. Thyrocytes produce and secrete Tg via the apical membrane into the colloid lumen whereas this 660 kDa glycoprotein, located on chromosome 8, provides the molecular matrix for thyroid hormone biosynthesis and storage in the colloid [4]. Thyroxidases (ThOx1/2), members of the NADPH oxidase family, are localized at the apical membrane; they provide H_2O_2 via a two-step-mechanism [5] which is necessary for the oxidation of iodide to atomic iodine catalyzed by thyroperoxidase (TPO) while atomic iodine iodinates tyrosine residues of Tg immediately. The iodinated tyrosine residues of Tg undergo oxidative coupling to yield predominantly T4 (L-thyroxine) and to a minor amount the biologically active form T3 (3,5,3′-triiodo-L-thyronine). Thyroid hormones are liberated by redox-regulated proteolytic release to the blood [6] where they bind to transport/distributor proteins: transthyretin (TTR; Ka $10^{10}\,M^{-1}$) [7,8], thyroxine-binding globulin (TBG; Ka $10^{8}\,M^{-1}$), and albumin (Ka $10^{6}\,M^{-1}$) [9,10]—they vary in capacity and affinity. TBG is a high affinity but low capacity transport protein, which is expressed in higher mammals only. TTR in contrast is a medium affinity and higher capacity binding protein with highly conserved regions while albumin binds T4 and T3 with low affinity and high capacity. Hence, free thyroid hormone concentration circulating in the serum is very low, below 0.1%.

In the periphery, thyroid hormones act on target tissues such as liver, kidney, heart, intestine, skeletal muscle, and brain. Action and metabolism of thyroid hormones require the uptake of iodothyronines across the plasma membranes via specific transporters. The most specific identified transporters are OATP1C1 of the Na-dependent organic anion transporter family and MCT8, which appear to be involved in T4 transport across the blood–brain barrier, and in T3 transport into brain neurons, respectively [11]. Especially, the multispecific organic anion transporter OATP14 (Slc21a14) which is widely expressed throughout the brain, except for the cerebellum, is involved in transport of thyroxine across the blood–brain barrier [12]. Moreover, amino acid transporters, in particular the L- and T-type amino acid transporters, have been shown to be involved in iodothyronine uptake into several tissues [13,14]. To exert biological action the prohormone T4 has to be converted to the active form T3, and this reaction is catalyzed by the intracellularly expressed deiodinases which are also characterized as common players of the selenoprotein family [15,16]. T3 exerts most of the thyroid hormone effects on development, differentiation, and metabolic pathways via binding to ligand modulated nuclear T3 receptors that are members of the nuclear hormone receptor family. Thyroid hormone receptors (TR) act as hormone-dependent transcriptional transactivators in the presence and as transcriptional repressors in the absence of thyroid hormone [17]. The TR genes *TRα*, *TRβ* and their isoforms are expressed in a wide variety of tissues, and although both main types of receptors are found in a given tissue, the relative expression levels of these isoforms differ considerably and determine cell specific response to T3.

Phenolic secondary plant metabolites, present in vascular plants and fruits, are ascribed various beneficial effects on health, for example cancer- and cardiovascular disease-preventing properties [18–20] and they are even administered for hormone-replacement therapy. On the other hand genistein, the major component of soy, was found to elicit uterine adenocarcinoma in adult mice after neonatal treatment (50 mg Genistein/kg/day) [21]. Furthermore, flavonoids are known to interfere with the thyroid hormone system – partly because of their structural similarity to thyroid hormones – but there is only limited knowledge concerning their mechanisms of