

COMMENTARY

Extrathyroidal thyroid hormone synthesis?

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Abstract

A paper published in this issue of the *Journal of Endocrinology* has revisited the hypothesis that thyroid hormones may be generated by tissues outside the thyroid gland in higher organisms including mammals. This commentary appraises the strengths and weaknesses of the study, the alternative explanations for the findings and possible future measures to

investigate further. The concept of extrathyroidal thyroxine and triiodothyronine synthesis has previously been proposed; by assuming that Nagao *et al.* and earlier authors are correct, the plausibility and possible mechanisms underlying the hypothesis are discussed.

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In a paper entitled ‘Influence of thyroidectomy on thyroxine metabolism and turnover rate in rats’, Nagao *et al.* (2011) have investigated thyroid hormone kinetics in the hypothyroid state.

In a number of carefully performed studies, which rely on a robust online solid-phase extraction liquid chromatography mass spectrometry (MS)/MS protocol developed by the authors to measure serum thyroxine (T₄), triiodothyronine (T₃) and reverse T₃, they demonstrate that serum levels of all three forms of iodothyronine are decreased but not completely ablated in thyroidectomised rats.

They postulate that deiodination of T₄ is enhanced by hypothyroidism to maintain levels of the biologically active thyroid hormone T₃ (Kohrle 2000). This could be verified by measuring deiodinase transcripts and enzyme activity in the peripheral tissues of the thyroidectomised rodents compared with euthyroid controls.

Their second, and more controversial, conclusion is that the low levels of thyroid hormone, which persist, are due to extrathyroidal production of iodothyronines. The more mundane explanation, that fragments of thyroid tissue remain, has been excluded by histopathological examination of the trachea, although radio-iodine uptake studies would have provided more solid re-assurance.

An alternative reservoir is reported in studies that indicate a role for the gut flora in absorbing and even deiodinating thyroid hormones (Distefano *et al.* 1993). To exclude this interesting possible source of the persisting T₄ and T₃, experiments could be conducted in rodents in which the intestinal bacteria had been reduced by antibiotic treatment.

Assuming that the authors are correct, and that thyroid hormones are produced outside the thyroid, how could this be realised? Thyroid hormone production requires a peroxidase enzyme, a source of iodine, a system to generate H₂O₂ and a substrate containing tyrosine residues (Vassart & Dumont 1992). In the mammalian thyroid, millennia of evolution have enabled the required components to be optimised in the form of thyroid peroxidase (TPO), the sodium iodide symporter (NIS), the dual oxidases (DUOX) and thyroglobulin (Tg), but alternatives exist.

TPO mRNA expression has been reported in extrathyroidal locations (Lai *et al.* 2006), but even if it is unique to the thyroid, lactoperoxidase or myeloperoxidase could provide very adequate substitutes. Iodide trapping is not restricted to the thyroid with breast, salivary gland, stomach and placenta being among the tissues in which convincing evidence for expression of a functional NIS exists (De la Vieja *et al.* 2000). Similarly, the dual oxidases DUOX1 and DUOX2 are widely expressed in tissues as diverse as the lung and the skin (Song *et al.* 2007) and even Tg has been detected in many regions; if iodinated, it is usually assumed to have a thyroidal origin (Lisi *et al.* 2002). However, if Tg is restricted to the thyroid might not any protein with appropriately placed tyrosine residues suffice? The Tg molecule is huge, yet the few tyrosines implicated as substrates for iodothyronine production are located at the extremities of the protein, no doubt where they can be accessed by TPO (Dunn & Dunn 1999).

It is generally accepted that invertebrates do not have a discrete thyroid gland and yet many such species use thyroid hormones, which may be ingested, form spontaneously or be

produced via catalysis. On the contrary, most vertebrates do possess a thyroid gland; although in the larval stages of the most primitive, thyroid hormones are produced by the endostyle (Crockford 2009); do the experiments of Nagao *et al.* hint at cells that could be considered to be a vestigial endostyle in higher organisms?

The notion of extrathyroidal hormone production is not new with authors from the sixties, and possibly earlier, providing solid evidence for the process (Evans *et al.* 1966, Taurog & Evans 1967, Obregon *et al.* 1981). Most recent evidence reports that *in vitro*, cardiomyocytes express all of the required components and are able to produce thyroid hormone (Meischl *et al.* 2008).

Thyroid hormones are essential to the development and maintenance of, for example, the brain and skeletal system and for regulation of the basal metabolic rate (Boelaert & Franklyn 2005); hence, it seems reasonable that higher organisms might have retained a back-up source. Although *in vitro* models can be very informative, it is hoped that Nagao *et al.* will extend their *in vivo* studies in a manner that will convince even the most sceptical thyroidologist and provide insight into the cells/tissues capable of this feat.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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