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Review

Genomic imprinting of the type 3 thyroid hormone deiodinase gene: Regulation and developmental implications ☆

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ABSTRACT

Background: In recent years, findings in a number of animal and human models have ignited renewed interest in the type 3 deiodinase (D3), the main enzyme responsible for the inactivation of thyroid hormones. The induction of D3 in models of illness and injury has raised critical questions about the physiological significance of reduced thyroid hormone availability in those states. Phenotypes in transgenic mice lacking this enzyme also point to important developmental roles for D3. A critical determinant of D3 expression is genomic imprinting, an epigenetic phenomenon that regulates a small number of dosage-critical genes in the mammalian genome. The D3 gene (Dio3) is imprinted and preferentially expressed from one of the alleles in most tissues.
Scope of review: In the context of the physiological significance of D3 and the characteristics and purported origins of genomic imprinting, we review the current knowledge about the epigenetic mechanisms specifying gene dosage in the Dio3 locus.
Major conclusions: Altered Dio3 dosage is detrimental to development, suggesting that the level of thyroid hormone action needs to be exquisitely tailored in a timely fashion to the requirements of particular tissues. An appropriate Dio3 dosage is the result of the coordinated action of certain genomic elements and epigenetic marks in the Dlk1-Dio3 domain.
General significance: The imprinting of Dio3 prompts intriguing questions about why the level of thyroid hormone signaling should be regulated in this rare epigenetic manner, and to what extent altered Dio3 expression due to aberrant imprinting may be implicated in human conditions. This article is part of a Special Issue entitled Thyroid hormone signalling.

1. Introduction

Thyroid hormones exert broad biological effects in all mammalian species. Their critical roles in the regulation of growth, development and metabolism are particularly remarkable, but most tissues express some form of thyroid hormone receptor and, thus, are a target for thyroid hormones. As a result, alterations in the mechanisms regulating the availability of thyroid hormone or its signaling have the potential to affect many physiological systems and, in humans, be the cause of developmental abnormalities and adult patho-physiological states.

Multiple factors, as reviewed in this special issue, influence the degree of thyroid hormone action that occurs in a given cell. One of them is the type 3 deiodinase (D3), a selenoenzyme that converts the two main hormones produced by the thyroid gland, the pro-hormone thyroxine (T4) and the active hormone triiodothyronine (T3), into metabolites with little or no biological activity [1–3]. Given this enzymatic activity, D3 is positioned to decrease T3 availability in the tissues in which it is expressed and, therefore, to reduce the local level of thyroid hormone action. The ample tissue profile of D3 expression, especially during development, suggests roles for D3 in multiple systems. This notion is being increasingly confirmed in animal models, adding physiological significance to the mechanisms regulating D3 expression.

In this regard, a puzzling observation about the D3 gene (Dio3) is that it is subject to genomic imprinting [4–6], an epigenetic phenomenon affecting a small number of genes that results in the preferential expression of one of the alleles [7]. This characteristic sets the D3 apart from other determinants of thyroid hormone action, and raises the possibility that the epigenetic mechanisms governing the allelic expression of Dio3 are an important determinant of thyroid hormone levels in tissues, and are critical to ensure normal development and physiology.

Here we briefly summarize past and recent observations about the physiological significance of D3, review the current knowledge about

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the genomic imprinting of Dio3 and the potential implications for human disease. We also briefly discuss its potential role in developmental plasticity, evolution and in the epigenetic inheritance of biological traits.

2. Pathophysiological significance of D3

Although a detailed account of this topic is not the focus of the present review, it is important to fully understand the impact that alterations in Dio3 expression could have on development and physiology. This will provide a context in which to evaluate the significance of Dio3 imprinting in health and disease.

The existence of the D3 (also called type III, 5- or inner-ring deiodinase) has been known for more than 30 years. Initially, D3 garnered less attention than the other deiodinase enzymes of the family, the type 1 (D1) and the type 2 (D2), as investigators were more interested in the activation of thyroid hormones, a process of particular importance in preventing the devastating effects that the lack of thyroid hormones exert on the central nervous system. At the time, it was simply – and rightly – assumed that D3 played a role in protecting tissue under circumstances of thyroid hormone excess, i. e., as a result of hyperthyroidism due to pathology of the thyroid gland, or during fetal development, a time when thyroid hormone levels are much lower than those in the mother.

Partially consistent with this hypothesis was the expression profile of D3, which exhibits a marked developmental pattern (Fig. 1A). D3 activity can be found in most tissues during fetal and early neonatal life [8]. In contrast, during adult life, high D3 expression is limited to the central nervous system [9–11], with lower expression levels found in the skin [12] and certain endocrine organs including the uterus, ovary and adrenal gland [13]. Most other tissues feature very little or no D3 expression in adulthood. For most tissues, D3 activity decreases one to two orders of magnitude from fetal life to adulthood (Fig. 1A). These observations, together with the very high expression of D3 in the placenta and pregnant uterus [14,15], suggested an important role for this enzyme during development and in the regulation of neural and endocrine functions.

As fetal development is a time of rapid cell proliferation and timely differentiation, it had been postulated that the high D3 expression at these stages was aimed at preventing tissues form undue exposure to thyroid hormones, a hypothesis consistent with the known roles of thyroid hormones in cell differentiation.

In this regard, a review on the role of D3 and other deiodinases in cell proliferation and differentiation and in signaling pathways related with these processes can be found in this issue [16].

2.1. D3 induction in fasting, illness and models of inflammation and injury

In the rodent, most adult tissues exhibit very low or undetectable levels of D3 activity. However, a number of physiological challenges, injuries and inflammatory processes can lead to remarkable inductions of D3 in certain tissues that would not express any D3 in a healthy state [17]. Thus, in humans and rodents, D3 is induced in the liver and skeletal muscle during critical illness [18–20] and after fasting [21,22]. These physiological states are typically associated with the "euthyroid sick syndrome", which is characterized by low levels of serum T3 and T4 despite the absence of any pathology in the hypothalamic–pituitary–thyroid axis [23]. Although the mechanisms underlying this syndrome are not fully understood, it is possible that an induction of D3 in certain tissues may contribute to this phenomenon.

In certain models of injury and inflammation, D3 expression can also be induced in tissues and cell types which would not normally express D3 in healthy conditions [17]. This type of D3 induction has been found in the heart when subjected to physiological insults such as myocardial infarction and pulmonary hypertension [24,25]. Induction of local D3 has also been observed in infiltrating cells during lung infection [26], after sciatic nerve lesion [27], and during chronic hind limb inflammation [28].

The clinical significance of this re-induction of D3 in adult tissues after an injury or physiological insult is largely unknown. The return of D3 expression in some tissues to levels that resemble those present early in development may reflect the need for new cell proliferation and differentiation processes to supply the cell needs and required endocrine microenvironment of the healing tissue. The increased D3 expression and the subsequently low local levels of thyroid hormones may be an integral component of the response to certain physiological challenges or necessary for optimal recovery. However, D3 induction in some of these models could just be a by-product of inflammation and potentially detrimental for health outcomes.

More studies are needed to determine in each of these models whether the role of D3 induction is adaptive or maladaptive, but this phenomenon may have important implications for human conditions, as it raises the possibility of clinical manipulation of the local or systemic thyroid hormone environment to foster recovery from illness and injury. In addition, the mechanism/s by which these conditions can induce D3 are unknown, but the susceptibility of this gene to expression dosage alteration in particular patho-physiological states may relate to its regulation by epigenetic mechanisms (see below) and warrants further investigation.

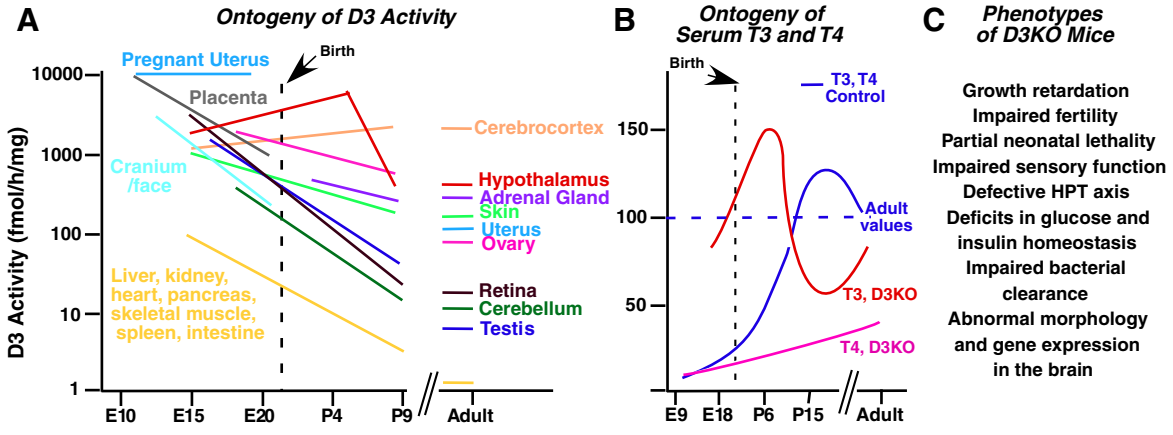

Fig. 1. Physiological significance of D3. A, Ontogeny and relative level of D3 activity in rodent tissues (patterns are approximate, based on cited literature). Note that D3 activity is reduced by one or two orders of magnitude in most tissues from fetal life to adulthood. B, Ontogeny of serum thyroid hormone levels in normal animals and in D3KO mice. During development D3KO mice are exposed to excessive levels of T3. Values are expressed as a percentage of normal adult values (horizontal dotted line). C, Summary of reported phenotypes in D3KO mice.