EDITORIAL

Deiodinases: keeping the thyroid hormone supply in balance

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Thyroid hormones (TH) are iodinated compounds that are required for the normal growth, development and function of nearly all vertebrate tissues. They do this by modulating the expression of many genes that are tightly regulated in a specific tissue- and time-dependent fashion. The primary mechanism of TH action involves the binding of 3,3′,5′-triiodothyronine (T_{3}) to its nuclear receptors in the context of regulatory TH response elements in target genes.

In humans, the thyroid produces the pro-hormone thyroxine (T_{4}), and only about 20% of the active hormone, T_{3}. T_{4} is largely inactive until it is deiodinated to T_{3} by the type 1 (D1) or 2 (D2) deiodinase. This reaction produces about 80% of the T_{3} present in the circulation in healthy subjects. A third deiodinase, D3, exerts an opposing function, i.e. it catalyzes inner ring deiodination, thereby inactivating T_{4} and T_{3}. Given these functions, D3 is considered the major physiological inactivator and terminator of TH action at peripheral level.

Why should we care about deiodinases and why they are so important? The role of deiodinases in TH homeostasis has become increasingly evident in the last 20 years, consequent to the cloning of the three members of the deiodinase family. A third deiodinase, D3, exerts an opposing function, i.e. it catalyzes inner ring deiodination, thereby inactivating T_{4} and T_{3}. Given these functions, D3 is considered the major physiological inactivator and terminator of TH action at peripheral level.

First, deiodinases are critical regulators of plasma T_{3} concentrations. This is observed daily in thyroidectomized patients in whom 1-T_{4} therapy suffices to guarantee normal plasma T_{3} levels. At a plasma level, deiodinases provide an important homeostatic mechanism, acting as the first line of defense when thyroid function is deranged or the supply of iodine is inadequate in order to maintain plasma T_{4} or, at a minimum, plasma T_{3} constant. It is not by chance that during hypothyroidism or iodine deficiency, the T_{3}-producing enzyme D2 is upregulated, while levels of the inactivating enzyme D3 is decreased. An opposite regulation occurs during hyperthyroidism, due to the remarkable feature that T_{4} itself is the most potent post-transcriptional inactivator of D2, while T_{3} rapidly induces the D3 enzyme at transcriptional level. Thus, the actions of deiodinases are integrated in a homeostatic mechanism designed to maintain tissue T_{3} content as normal as possible even in the face of altered serum hormone supplies.

Second, deiodinases control TH action in a precise spatio-temporal fashion, according to the needs of selected tissues and cells. The T_{4} concentration is generally quite stable in human plasma; even more stable is the T_{3} concentration. During fetal development, when low plasma T_{3} is necessary for the proper development and growth of fetal tissues, D3 is highly expressed in the placenta, the endometrium and in many embryonic tissues, with the consequence that free T_{3} is almost ten-fold lower in fetal versus maternal plasma, while reverse T_{3} is markedly increased.

Deiodinases are also tightly regulated in post-natal life when they are required to make local adjustments of intracellular T_{3} concentrations. A striking example is the expression of D2 and D3 deiodinases during maturation of the cochlea and during the onset of hearing. D3 is expressed in the early phases of cochlear development, and this is followed by a local, carefully timed but brief, burst of D2 activity in the cochlear precursor cells early post-natally. This is required to provide the proper amount of T_{3} necessary for cellular differentiation. This example seems to challenge the old concept that a given cell type expresses only one type of deiodinase. Emerging evidence indicates that in various cell contexts, D2 and D3 are expressed in a very dynamic balance, by which the expression of one enzyme coordinates with the other depending on the specific cellular needs at that specific time. Future work is necessary to understand all the signals governing the dynamic expression of selected deiodinases in specific cells.

Third, deiodinases allow the homeostatic mechanism of TRH/TSH regulation to occur at physiological level by ‘manipulating’ T_{4} concentrations in order to regulate TRH/TSH secretion. The generation of pituitary nuclear T_{3}, which is required for the homeostatic feedback regulation of TSH release, depends on a combination of T_{4} and T_{3}. D2 has a central role in this process that allows pituitary (and hypotalamic) cells to monitor both serum T_{3} and T_{4} independently and influence TSH secretion accordingly.
Finally, it is not inconceivable that deiodinases will be used as a molecular tool, i.e. to modulate deiodinase concentrations in a tissue-restricted manner. It may well be possible to deliberately manipulate intracellular T₃ concentrations in different tissues to achieve therapeutic goals, while not perturbing the normal TH concentrations in the remainder of the body.

These Thematic reviews on deiodinases contain an overview of recent data about the intricate regulation of deiodinase activity in the control of plasma and intracellular TH action, including what happens when the actions of deiodinases are altered and how this occurs in different clinical settings (Dentice & Salvatore 2011, Maia 2011, Williams & Bassett 2011). Despite progress in our improved understanding of the structure and function of the deiodinases, much more remains to be discovered. Deciphering these complex, interactive mechanisms is an exciting challenge and a promising source of information about how TH action can be so finely regulated in such a tissue-specific manner.

References


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