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Mammalian type 2 deiodinase sequences: finally, the end of the beginning.

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Editorial



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In this issue of The Journal, Croteau and her colleagues report the long-sought sequences and analyze the tissue expression of the rat and human Type 2 deiodinase (D2) mRNAs (1). This is the third, and probably last, member of the mammalian selenodeiodinase family to be identified. Where do we stand now in our knowledge of thyroid hormone activation and inactivation as catalyzed by these unusual enzymes? Type 1 deiodinase (D1) is expressed in the liver, kidney, thyroid, and pituitary and its action produces plasma 3,5,3'-triiodothyronine (T3) from thyroxine (T4) by 5'-deiodination via a high Km (2 µM T4) reaction which is sensitive to inhibition by 6n-propylthiouracil (PTU) (for review see reference 2). D1 can also 5-deiodinate T4 or T3-sulfate thereby inactivating them. Type 3 deiodinase (D3), a 5-deiodinase inactivating T4 or T3, is expressed in the central nervous system (CNS), placenta and in fetal epidermis (2). In all three deiodinases, the rare amino acid selenocysteine, encoded by UGA, is essential to efficient catalysis (2-4).

The realization that there was a second 5'-deiodinase came from in vivo studies showing that intracellular generation of T3 from T4 in the pituitary of the hypothyroid rat was not blocked by PTU and, therefore, was not catalyzed by D1 (5). Subsequently a low Km (2 nM T4), PTU-resistant 5'-deiodinase was also found in CNS, placenta and brown adipose tissue (BAT) (2). In hypothyroid rats, D2 activity increases while D3 and D1 are reduced. Excess T4 causes the opposite effect suggesting that the deiodinases are part of a peripheral homeostatic mechanism designed to keep the level of T3 constant even when T4 is reduced such as occurs during iodine deficiency. D2 is particularly intriguing since in the CNS, BAT, and pituitary, the T3 derived from D2-catalyzed T4 5'-deiodination accounts for most of the nuclear receptor bound ligand (2). Interestingly, while both D1 and D3 are regulated by T3 at a transcriptional level, until the present, D2 activity was thought to be controlled primarily by the effect of T4 to accelerate inactivation of the enzyme by a posttranslational mechanism.

Several unexpected results of Croteau et al. have important implications for understanding mammalian thyroid physiology. First, as testimony to the value of comparative endocrinology, the rat D2 was identified by probing with the *Rana catesbeiana* D2 which was, in turn, recently cloned using information from earlier studies of amphibian deiodinase physiology (4). The first surprise is that D2 mRNA is not only found in the tissues expected from earlier studies, but is also present in human (but not rat) skeletal and cardiac muscle. Recent studies show D2 activity in human skeletal muscle is sufficiently high that it could provide significant quantities of circulating T3 explaining the presence of a PTU-insensitive pathway for peripheral T3 production in humans (6). Second, Croteau et al. demonstrate that negative regulation of D2 by T4 also occurs at a pretranslational level. In hypothyroid pitu-

J. Clin. Invest. © The American Society for Clinical Investigation, Inc. 0021-9738/96/07/0242/02 \$2.00 Volume 98, Number 2, July 1996, 242–243 itary, BAT, and CNS, D2 mRNA is increased but remarkably more so in BAT and pituitary (1). The authors speculate that while negative transcriptional regulation by T4 is important in these two tissues; in CNS, post-translational regulation may predominate. The critical role played by D2 in BAT function is re-emphasized by finding a marked increase in D2 mRNA during cold stress. If D2 does not increase, the cold-exposed rat dies of hypothermia due to the inability of BAT to generate sufficient intracellular T3 to permit maximal synthesis of uncoupling protein. A similar stress occurs at the time of delivery in the human neonate which also expresses D2 in BAT (2).

Since the iodothyronine deiodinases all contain selenocysteine, how does the cell distinguish between the UGA encoding this amino acid and a UGA "stop" codon? In prokaryotes, a stem-loop structure is present in the coding region of the selenoprotein mRNA which allows the association of the selenocysteinyl tRNA and a specific elongation factor (for review see reference 2). In eukaryotes, these stem-loop sequences, termed selenocysteine insertion sequence (SECIS) elements are present in the 3'-untranslated region of selenoprotein mRNAs (2, 3). SECIS elements which have similar structure and are functionally interchangeable are present in all eukaryotic selenoprotein mRNAs identified to date including those encoding human D1, D3, and Rana catesbeiana D2. They are usually found within 2 kb of the selenocysteine codon (2, 3). However, Croteau et al. found no SECIS activity in either of the 1.9-kb partial cDNAs of the mammalian D2s. A heterologous SECIS element from rat D3 was inserted into the vector to permit transient expression. Presumably the D2 SECIS element is located further 3' in these 6-8-kb mRNAs. The mammalian D2 mRNAs are also much larger than the roughly 2 kb D1 and D3 messages or that of the 1.5-kb Rana D2. However, the D2 story is even more complicated in that there is a second inframe UGA codon near the end of the open reading frame in the mammalian D2. Does this UGA encode selenocysteine or signal "stop"? The presence of two 75Se labeled bands of appropriate sizes in cells transiently expressing human D2 suggests that both could be true (6).

As implied by the title of this Editorial, the availability of the D2 cDNA sequence will permit definitive studies of the developmental and hormonal regulation of D2 expression, a comparison of the mechanism for specific 5'-deiodination by D2 with the similar, yet distinct, reactions catalyzed by D1 and D3 as well as an exploration as to how substrate inactivates the D2 protein. New insights into the mechanism of selenoprotein synthesis will no doubt come from studies of the D2 SECIS element and unraveling the significance of the second UGA codon and the shorter D2 transcripts in stimulated tissues. Lastly, combined studies using the cDNAs of all three deiodinases should permit an understanding of the mechanisms governing the coordinated regulation of thyroid hormone activation and inactivation in the intact vertebrate.

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