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Why We Should Teach Medical Students the Correct Model for Thyroglobulin Iodination?

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Editorial Note

The iodination of thyroglobulin (Tg) has been studied extensively over the past 50 years [1]. Neither textbooks nor the medical literature have coalesced around a model for iodination of Tg-bound tyrosyl residues. Published reviews on various aspects of thyroid hormones either avoid addressing the question or refer to Thyroid Peroxidase (TPO) catalyzing iodination Tg tyrosyl groups [2,3]. While the mechanistic details of enzyme-mediated biological reactions frequently do not influence clinical practice, we believe that the correct model for Tg iodination establishes (a) a chemical rationale for the evolutionary pressure leading to formation of the follicular lumen, (b) a mechanistic basis to contemplate adverse drug reactions in the thyroid, and (c) a logical basis to contemplate future exploration of Thyroid Hormone (TH) formation. It seems clear to us that the literature supports a model wherein TPO releases reactive intermediates into the follicular lumen including I_2 that are responsible for Tg iodination and formation of nascent thyronine.

Heme peroxidases catalyze the 2-electron reduction of hydrogen peroxide to water. The first step in this process is the binding of hydrogen peroxide to the ferric heme group in the active site. The next step(s) occurs via two sequential one-electron transfers or a single two electron transfer. The reducing equivalents to convert hydrogen peroxide into water can come from a wide range of small molecules e.g. iodide or tyrosine, which are referred to as donor molecules. The iodination of tyrosine by Lactoperoxidase (LPO), Myerloperoxidase (MPO) and Thyroid Peroxidase (TPO) has been studied using Michaelis-Menten kinetics to gain insight into TH synthesis. Most of these studies are problematic since I_2 released from the enzyme reacts with both water and hydrogen peroxide i.e., the reaction products react with substrates. Huwiler, et al. proposed a mechanism for tyrosine iodination that depends upon the concentration of reactants and reaction products [4-6]. This concept captures the essential point that TPO reaction products react with other substrates and/or chemicals in the environment. These extra-enzymatic reactions can influence or dominate the ultimate reaction pathways.

Kinetic data comparing chemical versus enzymatic iodination of human Tg demonstrate that enzymatic iodination does not confer any specificity versus direct chemical iodination [7,8]. That is, identical tyrosyl sites are iodinated by both chemical and enzymatic iodination of human Tg. This is the logical outcome for an iodination model that relies upon the reaction products from an enzyme reaction to effectuate iodination. The only differences observed between the enzymatic and chemical iodination of Tg is a slightly higher di-iodotyrosine content and a correspondingly lower mono-iodotyrosine content in enzymatically iodinated Tg. This small disparity is likely due to different ratios of HOI/I_2 in an enzymatic versus chemical iodination environment as a higher concentration of I_2 would be expected in the enzymatic iodination. In addition, both D-and L-tyrosine are enzymatically iodinated at the same rate.

Although the three-dimensional structure of human TPO is not available, its close phylogenetic relationship and high sequence homology with vertebrate and especially mammalian peroxidases (ranging from 40% to 70% residue identity) allow conclusions about binding constraints for potential donor molecules in TPO. Access to the active site in mammalian peroxidases is sterically hindered as the heme of mammalian peroxidases is in a crevice of about 15 A˚ in depth, a single open funnel-shaped channel that ranges from approximately 10 to 15 A˚ in diameter provides access to solvent. The substrate channel narrows before reaching the distal heme cavity that contains the amino acid triad histidine, arginine, and glutamine. This conserved triad participates in a rigid hydrogen bond network that involves water molecules and connects the heme cavity, i.e., the site of donor molecule oxidation, with the exterior channel. The 2.3 A˚ resolution X-ray structure of the MPO indicates that smaller aromatic donor molecules like salicyhydroxamic acid bound in the active site is tilted about 20˚ with respect to that of the heme pyrrole ring that forms the lower surface of the hydrophobic cavity, while the conserved arginine forms the upper surface. Salicyhydroxamic acid is hydrogen bonded to both the distal histidine and glutamine but is not coordinated to the heme iron. A similar binding site has been found also for indole derivatives by computational docking. A free tyrosine would bind in a similar manner [14]. The hydroxyphenyl group of a Tg-bound tyrosyl residue cannot reach this hydrophobic binding pocket.

Cryo-EM has dramatically improved our understanding of TH synthesis and unequivocally identified the complete set of tyrosines used at the four Tg hormonogenic sites [11]. TH formation occurs when the aromatic ring of a donor, di- or mono- iodo-tyrosine, is transferred to a proximal iodo-tyrosine acceptor, thereby forming a nascent thyronine still connected to the polypeptide backbone of Tg. While acceptor tyrosines at hormonogenic sites must be solvent exposed in order to be iodinated, acceptor-donor pairs must lie roughly antiparallel to each other and therefore the proximal acceptor tyrosine is further sterically shielded from direct interactions with external proteins. When we further consider that TPO is a membrane bound protein, it seems impossible that iodination of Tg-bound tyrosyl residues can occur at the active site of TPO but must occurs *via* freely diffusing iodination equivalents released from TPO.

Comparative studies demonstrate Tg iodination in the living representatives of protochordates from which vertebrates evolved. These species have a thyroid system; TH receptors, deiodinases, and THs exert pharmacologic activity. However, THs are not formed in a thyroid with a follicular lumen but in a more primitive homolog of the thyroid known as the endostyle. TPO is present in certain endostyle cells but Tg cannot be synthesized since its gene is absent from the protochordate genome. The question is why Tg, synthesized at considerable metabolic expense with no evidence of recycling of its peptide components, ends up as a keystone of vertebrate TH synthesis in a separate structure within the thyroid? An additional burden to this model exists, because <3% of synthesized TPO contributes catalytically to TH biosynthesis. While storage of iodine in an iodine-deficient freshwater environment cyclostomes, the most primitive extant vertebrates, may offer selective advantages, the chemistry that underlies synthesis of THs, i.e., iodination impose evolutionary constraints to the level of TH synthesis required for warm blooded animals. Iodination in primitive organisms is nonspecific and a synthetic strategy for TH formation in a biological matrix is constrained by the potential of many organic species to react with oxidized iodide species. The exclusion of extraneous proteins and lipids from the lumen other than Tg which represents 37% of the protein present in the lumen provides an environment that allows freely diffusing iodination equivalents to react primarily with the tyrosyl groups of Tg.

Rather than evolve a pathway for TH synthesis, vertebrates evolved a physical structure that provides an environment that optimizes the chemical iodination of Tg; that is, the lumen can be envisioned as a biological test tube. It seems to us that teaching this model to medical students would provide them with a mechanistic basis to consider adverse events from supplements or drugs can interfere with TH synthesis [12-14].

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