Iodine Metabolism and Thyroid Physiology: Current Concepts

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ABSTRACT

Iodine plays a central role in thyroid physiology, being both a major constituent of thyroid hormones (THS) and a regulator of thyroid gland function. This review concerns those aspects of thyroid physiology in which significant advances have been made in recent years. We have known for decades that the thyroid gland concentrates iodide (I\(^-\)) against an electrochemical gradient by a carrier-mediated mechanism driven by ATP. A similar I\(^-\) uptake mechanism is found in other organs, including salivary glands, stomach, choroid plexus, and mammary glands, but only in the thyroid does TSH regulate the process. This past year saw a major advance with the cloning of the thyroid I\(^-\) transporter. This development opens the way to an elucidation of the regulation of I\(^-\) transport in the normal gland and in thyroid neoplasms that lack this property ("cold" nodules). All of the subsequent steps in TH biosynthesis, from oxidation and organification of iodide to the secretion of T\(_4\) and T\(_3\) into the circulation, are stimulated by TSH and inhibited by excess iodine. Recently, some of the regulatory mechanisms have been clarified. The function of the major TH-binding proteins in plasma is to maintain an equilibrium between extracellular and cellular hormone pools. Transthyretin, the principal T\(_4\)-binding protein in cerebrospinal fluid, may play a similar role in the central nervous system. Although it generally is agreed that cellular uptake of TH is a function of the unbound (free) form of the hormone, there is evidence that certain TH-binding plasma proteins (i.e., apolipoproteins) may serve specific transport functions. The intracellular concentration of T\(_3\), the active TH, is determined by the rates of cellular uptake of T\(_4\) and T\(_3\), the rates of metabolic transformation, including conversion of T\(_4\) to T\(_3\), and the rate of T\(_3\) efflux. The latter has been assumed to be a passive process. However, recent studies by our group in San Francisco have shown that T\(_3\) is transported out of cells by a specific, saturable, verapamil-inhibitable mechanism. This T\(_3\) efflux system is widespread among cells from many tissues and, at least in liver, modulates intracellular and nuclear concentration of the hormone and thereby influences TH action.

INTRODUCTION

Iodine plays a central role in thyroid physiology, being both a constituent of thyroid hormone and a regulator of thyroid gland function. This is a brief survey of iodine metabolism and thyroid hormone physiology, focusing selectively on some significant recent advances and citing when possible reviews rather than primary references.

Dietary iodine is absorbed efficiently in the gastrointestinal tract. Iodine in organic form is converted mostly to iodide before absorption. Fig. 1 shows a compartmental model of iodide distribution in the human, based in part on the work of Hays (1,2). Plasma iodide exchanges rapidly with iodide in red blood cells and with both rapid and slow extracellular compartments. Besides the thyroid, other organs that concentrate iodide include the salivary glands, gastric mucosa, choroid plexus, mammary glands, and the placenta. The enteric phase consists of iodide secreted into saliva and gastric juice, which moves into the small intestine for reabsorption. The kidneys account for about two-thirds of the iodide cleared from the plasma and more than 90% of iodide excreted from the body. Sweat and breast milk account for variable fractions of iodide loss. Hays (3) has presented evidence that iodide is secreted from the blood into the large bowel, which may explain partly why the colon often is seen in radiiodine scans in patients post-thyroidecctomy. However, the fecal route contributes only about 1% of total body iodide clearance.
Fig. 1. A compartmental model of inorganic iodine distribution and clearance in humans, adapted from the work of Hays (1,2). The rates of exchange of iodide between compartments are given in % of the plasma iodide compartment transferred per minute. The rate of iodide transfer from stomach to small intestine is expressed as a mean transit time (T).

Fig. 2 shows a simplified schema of thyroid iodine metabolism (4). The follicular cell in situ displays functional and structural polarity; the iodide transporter resides in the basolateral plasma membrane, which also contains ATPases and various channels and receptors, including the TSH receptor (not shown). At the apical surface, thyroglobulin, thyroid peroxidase, hydrogen peroxide, and iodide all come together. Oxidation and organification occur at or near this cell-colloid interface. Hormone secretion involves, first, pinocytosis of colloid-containing iodinated thyroglobulin, then fusion of colloid droplets with lysosomes, followed by proteolysis, which liberates free moniodotyrosine (MIT), diiodotyrosine (DIT), T4, and T3. Iodotyrosine dehalogenase regenerates iodide from MIT and DIT for reuse within the thyroid or release into the blood, accounting for the iodide leak in the chronic state of iodine excess and in certain thyroid disorders. Type I iodothyronine deiodinase converts some of the free T4 into T3. Both hormones are released into the circulation by a process that is not well understood. The thyroid also

FIG. 2. A scheme of iodine metabolism and hormone biosynthesis in a single thyroid follicular cell. The vascular space is on the left, and the lumen of the follicle is on the right. The shaded box straddling the basolateral membrane represents the iodide transporter. At the apical surface, TPO stands for thyroid peroxidase, and H2O2 depicts the hydrogen peroxide generating system. 5'D is the Type I iodothyronine 5' deiodinase.
releases thyroglobulin, of which some is iodinated and some uniodinated, newly synthesized protein.

TSH stimulates every phase of thyroid iodine metabolism (5,6). Most of the effects of TSH are mediated by the G protein-adenylate cyclase-protein kinase A cascade. The TSH-induced stimulation of iodide uptake is a delayed effect and involves an increase in the maximum velocity of the iodide transport mechanism. This effect is blocked by inhibitors of RNA and protein synthesis, and therefore the TSH-induced stimulation of iodide transport has been assumed to involve increased gene expression (5). However, recent work suggests that the action of TSH may involve either translocation of the iodide pump from the interior of the cell to the plasma membrane or conversion of an inactive form of transporter in the plasma membrane to an active form (7). TSH also increases ATP production and ATPase activity. One of the earliest effects of TSH is to open the apical iodide channel to increase iodide efflux from cell to colloid. TSH increases the synthesis of thyroglobulin and thyroid peroxidase, via the cyclic AMP (cAMP) cascade acting at the level of transcription and possibly post-transcription as well. The stimulation of hydrogen peroxide production appears to involve the inositol phosphate-calcium pathway at least in the human thyroid.

The stimulatory effects of TSH on pinocytosis, proteolysis, and Type I deiodinase can be reproduced by cAMP. Secretion of thyroglobulin also is under TSH control (via the cAMP second messenger pathway). All of these manifold effects of TSH on thyroid function, of course, are mimicked by the stimulating anti-TSH receptor antibody of Graves' disease.

The supply of iodine regulates thyroid hormonogenesis and alters thyroid sensitivity to TSH. This has been termed "autoregulation" (8,9). Excess iodine exerts generally inhibitory effects, most of which are mediated by one or more still unidentified organic iodine compounds, probably iodolipids. There is a blunting of all TSH effects mediated by both second messenger cascades. The Wolff-Chaikoff effect, which is an acute iodine-induced inhibition of organification, appears to be mediated by decreased hydrogen peroxide production. Other effects of excess iodine include down-regulation of iodide transport, responsible for the escape from the Wolff-Chaikoff effect; increase in the ratio of iodothyrosines to iodothyronines in thyroglobulin; and acute inhibition of pinocytosis and proteolysis, resulting in decreased hormone secretion. This inhibition of colloid resorption, which involves steps both pre- and post-cyclic AMP, is the only effect of iodine shared by lithium (10).

Thyroid iodide uptake is basic to the clinical applications of radiiodine in diagnosis and therapy. Work in the early 1960s established that the thyroid iodide transport is saturable and specific and is linked to a sodium-potassium ATPase (11). It was shown subsequently that the driving force for iodide uptake against the electrical gradient is the transmembrane difference in sodium ion concentration generated and maintained by the sodium-potassium ATPase. The iodide pump itself is actually a sodium-iodide cotransporter, or symporter. Two sodiums are transported for each iodide ion that moves into the cell. Complex anions, such as perchlorate, competitively inhibit the iodide transporter. These and many other properties have been known for years, but until recently no one had isolated the iodide transporter.

The cloning of the rat sodium-iodide symporter is a major step forward (12). The putative structure of the rat sodium-iodide transporter, deduced from the nucleotide sequence of the isolated cDNA, includes 618 amino acids, 12 putative transmembrane domains, 3 charged residues, including an arginine in the sixth helix, and a consensus sequence for protein kinase A phosphorylation on the final intracellular loop near the carboxy-terminus. Jhiang and colleagues, using the cDNA sequence of the rat iodide transporter, recently isolated and cloned the human homologue (13). We now may expect rapid progress in finding answers to such questions as: What is the basis for the defect in iodide transport in "cold" nodules? What is the molecular mechanism by which TSH stimulates iodide transport in differentiated thyroid cancers?

Normal thyroid tissue incubated in vitro under conditions in which organification of iodine is blocked can generate a tissue-to-medium iodide gradient of 10 to 1 or more, whereas most solid cold thyroid nodules, both benign and malignant, are unable to generate any gradient at all (14,15). However, not all cold nodules show this type of defect. Some neoplasms concentrate iodide but cannot organify it (16). Either defect will shorten the effective half-life of iodine in the tumor. Goitrous or neoplastic thyroids may produce thyroglobulin abnormal in structure and iodine content (17,18). In addition, some tumors may produce large amounts of smaller iodinated proteins, like iodoalbumin. Rare cases of hyperthyroidism due to overproduction of hormone by differentiated thyroid carcinoma have been described. Perhaps these involve somatic mutations in the TSH receptor or G protein causing constitutive activation, similar to the activating mutations described in some toxic adenomas (19).

The physiologic role of plasma protein binding has been the subject of speculation ever since the discovery of thyroxine-binding globulin (TBG) in 1952. Robbins and Rall, who formulated in mathematical terms the free hormone hypothesis, postulated that plasma binding proteins, TBG in particular, provide a circulating reservoir of thyroid hormone and a buffer against drastic and abrupt changes in free hormone concentration. None of the three major thyroid hormone binding proteins (TBG, transthyretin, and albumin) is essential for life (20).

Further insight and support for the free hormone hypothesis was provided by Mendel and colleagues (21), using a liver perfusion system to show that, in the absence of any binding protein in the perfusing medium, both T₄ and T₃ are taken up rapidly and retained by the first cells encountered. In contrast, in the presence of binding protein, hormone is distributed uniformly throughout the organ. Thus, the binding proteins, by limiting the fractional uptake into cells, ensure equilibrium between cellular and extracellular compartments. It has been suggested that transthyretin, which is the major T₄ binder in the cerebrospinal fluid, may play a similar role in ensuring uniform distribution of the hormone throughout the central nervous system (20).

These considerations do not exclude the possibility that certain binding proteins may target hormone to specific
sites in the body. For example, Benvena and Robbins (22) have shown that human apolipoproteins mediate the uptake of T4 (but not T3) by fibroblasts containing low-density lipoprotein receptors. We do not yet know the physiologic importance of this type of cellular uptake mechanism.

The intracellular T3 concentration largely determines the degree of occupancy of nuclear T3 receptors and thereby regulates the biologic responses to thyroid hormone (23). Some factors that determine intracellular T3 concentration are the rates of uptake of T4 and T3 from the extracellular fluid by passive diffusion or via stereospecific, energy-requiring uptake mechanisms (24). Further, the hormones undergo conjugation, oxidative decarboxylation, and deamination, but the major metabolic pathway is deiodination, which results in either activation or inactivation of hormone and plays an important role in overall thyroid hormone economy and in modulation of thyroid hormone levels in specific tissues.

The deiodination of iodothyronines is carried out by a family of selenoprotein enzymes. The Type I enzyme was cloned in 1991 (25). Subsequently, the Dartmouth group reported the cloning of the Type III deiodinase (26) and, recently, the human and rat Type II enzyme (27). In the euthyroid individual the Type I enzyme, present in liver and kidney, converts T4 to T3 and, even more efficiently, reverse-T3 to T2. The sulfoconjugates of T4 and T3 are preferred substrates for 5-deiodination by the same enzyme. The Type II 5'-deiodinase generates T3 from T4 in brain, pituitary, and brown adipose tissue. Recent data from two laboratories indicate that in the human (but not the rat), cardiac and skeletal muscle contain Type II deiodinase and may be a major source of circulating T3 (27,28). The Type III 5-deiodinase converts T4 and T3 to their inactivederivatives and thus modulates the T3 level in the brain and serves to protect the fetus from excessive amounts of the hormone (29).

In the low-T4 state, the Type I (in liver and kidney) and Type III are down-regulated and Type II activity is increased, thereby tending to conserve T3 in vital organs, such as the brain. The exception is the Type I enzyme in the thyroid, which becomes more active, accounting in part for the high ratio of T3 to T4 secreted from the TSH-stimulated gland, as, for example, in early thyroid gland failure (29).

Finally, the rate of efflux of hormone from the cell theoretically can affect the steady-state cellular T3 level. Few studies have addressed outward transport as a process distinct from uptake, and until recently there have been no data indicating that thyroid hormone efflux is carrier-mediated or that it can affect hormone action.

Ribeiro and colleagues (30) recently have published evidence that in mammalian cells a saturable, specific, temperature-sensitive, verapamil-inhibitable T3 efflux mechanism influences cellular T3 concentration and responsiveness to T3, presumably by controlling access of the hormone to nuclear receptors. The T3 export process was demonstrated initially in rat hepatoma cells, which were adapted specially for resistance to a bile acid ester and which overexpress several apparently novel ATP-binding cassette (ABC) proteins of the family of multi-drug resistant (MDR) P-glycoproteins. Verapamil-inhibitable T3 efflux also was found in primary rat hepatocytes, cardiocytes, and fibroblasts. In hepatoma cells and primary hepatocytes, verapamil had no effect on T3 uptake. The reverse inhibition by verapamil suggests that one or more ABC/MDR-related proteins are involved. These results suggest that T3 extrusion from cells is a regulated process distinct from T3 entry, providing an additional mechanism that, by controlling access of thyroid hormone to nuclear receptors, influences hormone action (30).

Virtually all of the advances in thyroid physiology made during the past half-century—from the first quantitative measurements of radioiodine uptake by the thyroid gland to the subsequent discovery of T3 and the demonstration of the complex regulation of thyroid hormone synthesis, secretion, transport, cellular metabolism, and hormone action—were possible because of the availability to investigators of radioiodine tracers.

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