Environmental Health Perspectives
Vol. 38, pp. 65-70, 1981

Factors Altering Thyroid Hormone Metabolism

by Jacob Robbins*

Thyroxine, the major secretory product of the thyroid gland, is metabolized in the peripheral tissues by phenolic conjugation, deamination, decarboxylation, and a cascade of monodeiodinations. This brief review focuses on the deiodination reactions, which currently are under intensive investigation. One product, 3,5,3′-triiodothyronine (T_3), is the major active form of the thyroid hormone, and about 80% of the T_3 produced in the body is derived extrathyroidally. Furthermore, a greater fraction of the T_3 found on nuclear receptors in pituitary and brain cells is derived intracellularly, as compared to liver and kidney cells. The latter tissues, on the other hand, appear to be the source of most of the circulating T_3. Another deiodinase, acting on the nonphenolic ring of T_4, gives rise to the hormonally inactive 3,3′, 5′-triiodothyronine ("reverse" T_3 or rT_3). A number of physiological and pathological events perturb the deiodination pathway, leading to a decrease in T_3 neogenesis and reciprocal changes in the circulating level of T_3 (which decreases) and rT_3 (which increases). This so-called "low T_3 syndrome" is also produced by a number of pharmacological agents. The biological effects resulting from these changes are incompletely understood, but they are potentially important in the body's adjustment to stress and as a site of action of toxic agents. In addition, they are of obvious importance clinically because of their influence on serum T_3 and TSH levels, which are commonly used tests of thyroid function.

The thyroid hormone after secretion from the thyroid gland undergoes a number of metabolic transformations (*1*). Although these were discovered and intensively investigated more than 25 years ago, there was relatively little interest in the subject until quite recently. Figure 1 shows the diphenyl ether structure of the major secretory product, thyroxine (T_4). Triiodothyronine (T_3), lacking the 5′-iodine, is secreted in much smaller quantity. One type of metabolic transformation takes place at the phenolic hydroxyl group of the so-called beta ring of T_4 or T_3. This consists of esterification by glucuronic acid or sulfate and occurs primarily in the liver and also in the kidney. The result is inactivation and excretion of the hormone. Pharmacological agents such as phenobarbital (*2*) and polychlorinated biphenyls (*3*), and environmental influences such as cold exposure (*4*), can affect these conjugation reactions and thus perturb hormone disposal and, secondarily, hormone secretion. However, I will not discuss these reactions further in this presentation. Another group of reactions occurs at the alanine side chain of the inner or alpha ring. This involves deamination and decarboxylation leading to the so-called acetic acid analogs which are metabolically active. At the present time, little is known about the quantities produced or about their contribution to hormone action.

The third metabolic route involves removal of the iodine atoms from the benzene rings. Formerly, this was thought to be a concerted deiodination leading only to iodide and the inactive thyronine molecule. It is now recognized, however, that stepwise deiodination is the major route of hormone metabolism. This process also leads to both active and inactive metabolites and is now the subject of intensive investigation. It has also become clear that these monodiodination reactions are influenced by a number of physiological and pathological events. In this account, I will discuss the deiodination reactions and in particular will review some of the information which has come to light about pharmacological effects on these reactions.

Removal of one of the outer ring iodines of

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*Clinical Endocrinology Branch, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20205

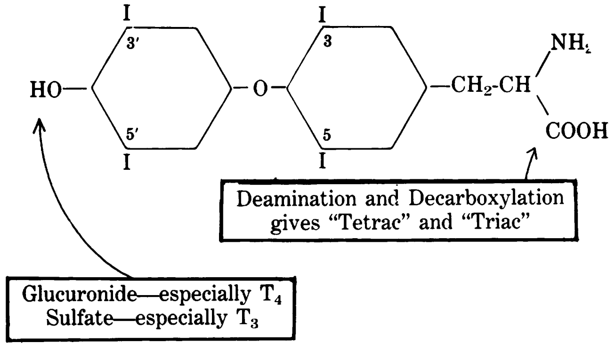


FIGURE 1. Structure of thyroxine (3, 5, 3', 5'-tetraiodo-L-thyronine) and metabolic reactions at the phenolic hydroxyl and the alanine side chain.

thyroxine leads to the formation of 3,5,3'-triiodothyronine, a compound which is biologically more active than thyroxine itself. On the other hand, removal of one of the inner ring iodines gives the so-called reverse triiodothyronine (3,3',5'-T_3 or rT_3) which is not only devoid of hormone activity but may actually have antihormone properties (*5*). Essentially none of the reverse triiodothyronine is derived from secretion *per se* by the thyroid gland.

Table 1 gives some quantitative data on the production and secretion rates of thyroxine and T_3 which have been derived from a recent investigation. It should be understood that these are approximate values, not only because of variations from one laboratory to another, but also because they are derived from kinetic studies which depend on complete hormone exchange between plasma and all tissues. It is now evident that T_3 equilibration does not occur in certain tissues, such as the pituitary and the brain (*7-9*). Nevertheless, it is clear that the major secretory product by far is thyroxine. On the other hand, the production rate of T_3 in the body is almost 1/2 that of thyroxine on a weight basis. From data such as these, it can be concluded that about 80% of the T_3 appearing in the body is the result of extrathyroidal monodeiodination of thyroxine and that almost half of the thyroxine secreted by the gland is utilized for T_3 formation.

Table 1. Production and secretion rates of the thyroid hormones.[a]

	Production rate, μg/day	Secretion rate, % of total PR
T_4	87	100
T_3	34	24
rT_3	36	2

[a] Data from Chopra (*6*).

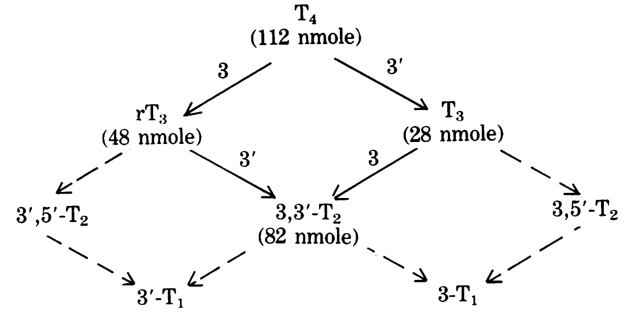


FIGURE 2. Monodeiodination cascade of the iodothyronines. The values in parentheses are the production rates of T_4 in intact man (*6*) or for T_4 derivatives in three athyreotic subjects receiving full T_4 replacement (*10*). Other data give a somewhat higher value for T_3 generated from T_4 (see Table 1).

Since T_3 is hormonally more active than T_4 and may in fact account for most of thyroxine's biological activity, we can conceive of thyroxine as a prohormone.

Figure 2 shows the cascade of monodeiodinations which are now known to occur after thyroxine is secreted from the gland. The arrows pointing to the right indicate removal of iodines from the outer ring while those pointing to the left indicate removal of inner ring iodines. It now appears that two deiodinases carry out all these reactions; i.e., 3' or 5'-deiodinase and 3 or 5-deiodinase. As can be seen from the production rates in terms of nanomoles per day, similar amounts of T_3 and reverse T_3 are formed and both are channeled through further deiodination to form 3,3'-diiodothyronine, an inactive metabolite. It is of interest that, whereas the molar ratio of T_4 to T_3 production is about 4, the molar ratio of T_4 to T_3 concentration in the plasma is approximately 60. This is the result of the very much more rapid disappearance rate of T_3 from the circulation, which is at least in part due to its lower affinity for the plasma transport proteins which bind the thyroid hormones.

Table 2 shows that there is very much more thyroxine than triiodothyronine in the extrathyroidal pool but that its distribution volume is considerably smaller than that of T_3 (*11, 12*). Furthermore, whereas thyroxine is almost equally distributed between the plasma, where it is bound to the transport proteins, the rapidly turning over hepatic and renal pools, and the more slowly turning over muscle, brain and other tissues, the bulk of triiodothyronine is found in the latter tissues. I should state again, however, that these data are based on the assumption that equilibrium exists. As already indicated, this assumption is not strictly correct, at least for T_3.

Table 2. Extrathyroidal distribution of the thyroid hormones.[a]

	T_4	T_3
Distribution volume, liters	12	31
Extrathyroid pool, μg	930	40
Plasma, %	22	18
Liver, kidney, %	31	5
Muscle, brain, skin, %	44	75

[a] The data are from primary sources discussed elsewhere (*1*).

A recent development of considerable interest is illustrated by the work of Obregon et al. (*8*). They administered simultaneously T_4 and T_3, labeled with two different iodine isotopes, either by repeated injection or continuous infusion over a period of five days. They then measured the T_3 in various tissues which was labeled by each of the isotopes. If all of these tissues were in equilibrium with the plasma, they would have found identical isotope ratios. In fact, the ratios varied widely from tissue to tissue. It is of interest that the brain had the highest proportion of T_3 derived from intracellular T_4 rather than from plasma T_3. This indicates clearly that the relative amounts of thyroxine and its metabolites found in the plasma do not necessarily reflect the proportions in a particular tissue where the hormone is exerting its biological effects.

Related information was developed in Larsen's laboratory (*7*, *9*) in greater detail. Again using T_4 and T_3 labeled with different iodine isotopes, these workers examined the T_3 sequestered in the cell nuclei where at least one of the hormone's biological receptors is known to exist. The fraction of nuclear T_3 which was derived locally within the tissue by monodiodination of T_4 was compared with that reaching the tissue by diffusion from the plasma. In the pituitary, half of the nuclear T_3 was derived locally, whereas in the liver this was only 1/4 and in the kidney it was 1/7. In the cerebral cortex, 3/4 of the nuclear T_3 was derived locally from T_4. T_3 in brain synaptosomes is also derived locally (*13*). Some of the implications of these very important experiments will be discussed later.

With this brief background on the deiodinative metabolism of the iodothyronines, I now want to describe some of the evidence which has come to light concerning a number of factors which operate to alter the amount of hormone moving through the various channels of metabolism. Table 3 lists several which I have labeled "physiological" only to differentiate them from the effects of various diseases and pharmacological agents which I will discuss later. One of the most striking variations is that seen in the fetus where there is a very marked reduction in the plasma level of T_3 and in the formation of T_3 from T_4 (*14*, *15*). At the same time, there is a relative increase in the plasma level of reverse T_3. As will be seen, a general phenomenon which runs throughout these observations is that T_3 and reverse T_3 are reciprocally related. Initially, this was believed to be the result of opposite changes in production of T_3 and rT_3 from their common precursor, T_4. It is now felt that it is more likely the result of a modification only in the 5′-deiodination pathway, which simultaneously decreases the production of T_3 and decreases the degradation of rT_3. However, alterations in rT_3 production also may occur under come circumstances. In the fetus, there is very little secretion of TSH until after birth, perhaps related to variations in T_3 production within the thyrotrophic cells (*16*).

Table 3. "Physiological" factors affecting T_4 deiodination.[a]

	T_3	rT_3	TSH
Age			
Fetus	↓↓	↑	↓
Old age	↓		N↓
Fasting (carbohydrate)	↓	↑	N
Cold exposure	↑		

[a] The arrows indicate the direction of changes in plasma levels, which can reflect changes in formation or degradation or both. All of these conditions decrease peripheral conversion of T_4 to T_3 except cold exposure.

A second phenomenon listed on this figure is seen in adults who are subjected to food deprivation, particularly carbohydrate (*1*, *17*). This also is associated with a decrease in 5′-deiodination of thyroxine and an increase in plasma rT_3 (*18*). It is of interest here that TSH secretion and its circulating levels are generally normal. This is quite unlike the finding when circulating T_3 is lowered as a result of hypothroidism. In that case, there is a compensatory increase in the production of TSH from the pituitary. Since the serum thyroxine level is relatively normal in fasting but not in hypothroidism, this leads to the question as to whether the pituitary can respond to thyroxine as well as to T_3. I will have more to say about this later.

Table 4 lists several diseases which are also known to result in alterations in thyroxine deiodination (*1*, *19*, *20*); they include liver disease, kidney disease and a variety of systemic illnesses of at least moderate severity. Surgical or other types of severe stress can also be included here. All of these are associated with diminished conversion of thyroxine to T_3 and decreased circulating levels of T_3. Reverse T_3 levels are generally either normal or increased and TSH production is usually normal. Furthermore, the patients are clinically euthyroid despite serum T_3 levels which are frequently in the hypothyroid range. Collectively, these conditions have been called the "low T_3 syndrome." From the standpoint of clinical medicine, they are perhaps more important for their perturbation of the tests of thyroid function than as an indicator of abnormal thyroid function requiring therapy. However, we still have much to learn about the clinical significance of these alterations in T_3 production.

The last two items in Table 4 concern hypothyroidism and hyperthyroidism. Very recent work has shown that the deiodination of thyroxine in the liver and in the pituitary and brain in these disorders is quite different (*16, 21, 22*). In hypothyroidism, there is a decreased formation of T_3 in the liver, but an increased formation in the pituitary and brain. In hyperthyroidism, the findings are the opposite. In fasting, on the other hand, it was found that hepatic formation of T_3 from T_4 is reduced while it is normal or only slightly decreased in the pituitary (*21*). These findings bear on the question of how the rate of pituitary TSH secretion relates to a particular circulating level of T_3 (*16*), since it appears to respond to the sum of intracellularly and extracellularly derived T_3.

I now want to move on to the subject which is central to the purpose of this symposium, and to discuss the effects that pharmacological agents can have on thyroid hormone deiodination. Table 5 summarizes results obtained with four drugs that have been studied extensively in man as well as experimental animals. In many of these experiments, the use of hypothyroid subjects on therapy, or euthyroid subjects in whom thyroid gland function is replaced by T_4 administration, has demonstrated that the findings I will discuss are largely, if not entirely, the result of alterations in peripheral T_4 metabolism.

Corticosteroid administration (e.g., 8 mg of dexamethasone per day) (*23, 24*) results in a prompt fall in circulating T_3, occurring within hours. This is due to an inhibition of its formation from thyroxine. At the same time, there is an increase in plasma reverse T_3. It is quite possible that some of the alterations observed in acute illness or stress, discussed above, may result from an increase in corticosteroid secretion.

Table 4. Diseases affecting T_4 deiodination.[a]

	T_3	rT_3	TSH
Liver disease	↓	↓↑[b]	↑N[b]
Nephrosis	↓	N	N
Systemic illness	↓	↑	↑N[b]
Hypothyroid	↓	↓	↑
Hyperthyroid	↑	↑	↓

[a] See footnote to Table 3.

[b] The more common findings when more than one is indicated.

Table 5. Drugs affecting T_4 deiodination.[a]

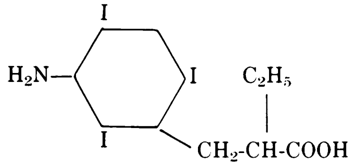
Drug class	Example	T_3	rT_3	TSH
Corticosteroid	Dexamethasone	↓	↑	↓
Thiourylene	Propylthiouracil	↓	↑	↑
Cholecystographic agent	Iopanic acid Ipodate	↓	↑	↑
Other	Amiodarone	↓	↑	↑

[a] See footnote to Table 3.

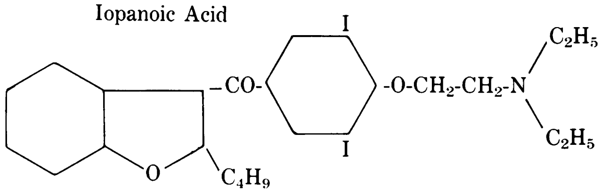
The second agent listed is the thiourylene drug, propylthiouracil (PTU). It was shown some years ago that certain antithyroid drugs, PTU being one, resulted in a slowing of thyroxine metabolism as well as a decrease in its hormonal effect (*4*). The other commonly used antithyroid drug, methimazol, does not have this effect. More recent experiments from a number of laboratories have clearly shown that PTU and its congeners interfere with the formation of T_3 in the peripheral tissues (*1, 16, 25, 26*). Again, reverse T_3 in plasma is increased. However, whereas 5′-deiodination of T_4 is decreased by propylthiouracil in liver, in the pituitary gland T_3 formation from T_4 is unaffected (*7, 16*). This may be due to a failure of propylthiouracil to enter the pituitary cells (*27*). In studies with tissue homogenates, it has been shown that PTU is a noncompetitive inhibitor of 5′-deiodinase (*28, 29*). Interestingly, it is much less effective in inhibiting 5-deiodinase (*30, 31*).

A third type of compound which has recently been shown to have a profound effect on thyroxine deiodination includes the radiographic contrast media, sodium ipodate (Oragrafin) and iopanic acid (Telepaque) (Fig. 3) which are commonly employed in cholecystography (*16*). These compounds markedly inhibit the conversion of T_4 to T_3 not only in the liver but also in the pituitary gland (*32-34*) and they are competitive inhibitors of 5′-deiodinase. It is of interest that other rather similar compounds may not have this effect on thyroxine metabolism. Since they result in an increase in serium reverse T_3, it is apparent that the 5-deiodinase is not severely impaired. An increase in TSH production occurs despite the fact that the drugs may result in a significant increase in the circulating thyroxine level. Furthermore, these changes in serum hormone levels are produced by a single oral dose of the radiographic contrast agent in routine cholecystography.

A fourth drug which affects thyroxine deiodination is amiodarone, a compound widely used in Europe as an antiarrhythmic and antianginal drug. Amiodarone causes a prompt fall in the circulating T_3 level and an even greater increase in circulating



Iopanoic Acid



Amiodarone

FIGURE 3

reverse T_3 (*35*). Thyroxine, on the other hand, remains constant and the changes in circulating T_3 are accompanied by an increase in TSH secretion. The mechanism of action of amiodarone has not been elucidated.

A fifth drug having similar, but less dramatic, effects is propranolol, a β-adrenergic blocking agent often used to treat hyperthyroidism (*1*, *16*, *36*). It appears that this action is unrelated to its anti-adrenergic effect.

To summarize the results on the drugs I have discussed, all of them cause a decrease in T_3 production from T_4 and a reciprocal increase in plasma reverse T_3 level. The effects on TSH production, on the other hand, are not the same for each agent. Amiodarone and especially iopanoic acid result in an elevation of TSH which, at least in the case of iopanoic acid, appears to result from a decrease of T_3 production from T_4 within the pituitary thyrotroph cells. In the case of corticosteroid administration, there is a decrease in TSH which probably results from an inhibitory effect of corticosteroid itself on the thyrotroph. In the case of propylthiouracil, TSH is increased even though it has been shown that this drug does not inhibit the formation of T_3 from T_4 within the pituitary cell. This indicates, as one might expect from the fact that half of the nuclear T_3 in the pituitary is derived from the plasma, that not all of the feedback inhibition of TSH secretion is by way of intracellular thyroxine metabolism.

In this discussion, I have attempted to review some of the recent developments in our knowledge of thyroxine deiodination. In particular, I have shown that this metabolism is affected by a number of rather different chemical agents, and we are just beginning to develop an understanding of the complexity of these metabolic events. It is clear that the extrathyroidal formation of T_3 from the T_4 which is secreted by the thyroid gland is the major pathway through which thyroid hormone exerts its effects. We now know that the kinetics of formation of T_3 is quite different in different tissues. Most studied have been the rapidly metabolizing tissues such as the liver and the kidney, which appear to be the major source of the circulating T_3, and the pituitary gland, which is the site of feedback control of thyroid secretion. Recent data indicate that the events in brain cells resemble more those in pituitary than in liver. We have also seen that different chemical agents can have different effects in the pituitary compared to the liver, and this is reflected in differences in TSH secretion, on one hand, and on T_3 circulating levels on the other. Still to be developed by further experimentation is an understanding of how the conversion of T_4 to T_3 is involved in hormone action in each of the tissues on which thyroid hormone exerts its effects. At this time, it seems likely that circulating T_3, originating in liver and kidney, may be the major source of active hormone for tissues such as muscle, whereas the circulating T_4 may be a more important source for pituitary and brain cells.

With respect to the subject of this conference, it is clear that these metabolic events affecting the thyroid hormone are potential sites of action of a variety of toxic agents. It is almost certain that in the near future many additional chemicals acting on these processes will be discovered.

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