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THE IMPACT OF NUTRITION ON THYROID HORMONE PHYSIOLOGY AND ACTION

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INTRODUCTION

Dietary iodine intake is of critical importance to thyroid hormone synthesis and secretion. Other aspects of nutrition also influence the thyroid and the thyroid hormones. These influences reflect adaptations in thyroid hormone

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physiology at multiple levels and in many organs including the hypothalamus, pituitary, thyroid, and several peripheral tissues. Presumably, they represent redundant, well-orchestrated metabolic changes. The same could be said of the alterations in thyroid hormone metabolism in patients with nonthyroidal illnesses for which the primary effects of the diseases are sometimes difficult to distinguish from the secondary effects of the altered nutritional state usually present.

Micronutrition and macronutrition can profoundly alter the synthesis, secretion, peripheral metabolism, and function of thyroid hormones. There is some evidence that vitamins, minerals, and other cofactors are important to the normal metabolism of thyroid hormones. Except for iodine, however, little is known of these requirements or of the physiologic or biochemical levels at which they operate.

In this review we focus on nutrition and not on disease, concentrating on macronutrition and thyroid hormone physiology and action. We review the impact of overnutrition, undernutrition, and diet composition on thyroid function at several levels of physiologic control.

THE HYPOTHALAMIC-PITUITARY AXIS

The regulation of thyroid hormones begins with neuroendocrine control of the thyrotroph within the pituitary. Thyroid releasing hormone (TRH) was the first hypothalamic-releasing peptide to be isolated, purified, and synthesized. It is a tripeptide (pyroglutamyl-histidylproline amide) and is widely distributed in the central nervous system, gastrointestinal tract, pancreas, testes, placenta, and amniotic fluid. In the adult rat, the highest concentrations are found in the pineal and hypothalamus, particularly in the median eminence. From the median eminence, TRH is secreted into the portal circulation of the anterior pituitary, where it stimulates the release and synthesis of thyroid stimulating hormone (TSH), enhancing both the alpha-specific and beta-specific subunits of TSH, particularly the distal glycosylation of preformed TSH. This action of TRH follows its specific high-affinity binding to a plasma membrane receptor. The mechanisms responsible for TRH-stimulated TSH secretion and synthesis are not yet clear. Hydrolysis of phosphatidylinositol followed by altered intracellular calcium is the proximate event in the secretion of TSH, while cAMP, which participates in many other systems, seems not to be involved.

TRH is the major stimulator and triiodothyronine (T_3) the major inhibitor of TSH secretion into the peripheral circulation. Both act primarily at the pituitary level, although there is now evidence that T_3 also acts at the hypothalamic level. Somatostatin and dopamine can inhibit TSH secretion at the level of the pituitary thyrotroph, but their effectiveness largely depends on

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the thyroid status; they are excellent inhibitors in hypothyroid subjects but have minimal effect in euthyroid subjects. Based on in vitro data, somatostatin and dopamine may also interfere with TRH release, but the physiologic significance of these findings is unknown. Of importance is that the pituitary and intracerebral concentrations of T_3 mainly depend on the local conversion of thyroxine (T_4) to T_3. In the euthyroid rat, most of the nuclear-bound T_3 in the pituitary comes from the local conversion of T_4 to T_3. A specialized enzyme (5'-deiodinase, type II) found in the CNS, pituitary, possibly adipose, and thermogenic brown adipose tissue (of rodents and possibly infants) is responsible for this conversion. This 5'-deiodinase has different characteristics from the 5'-deiodinase (type I) originally discovered in the liver and other peripheral tissues including the kidney and thyroid gland. Significantly, the K_m for T_4 is 10^{-3} orders of magnitude lower for the type II enzyme; and type II is different from the type I peripheral enzyme in that it is specific for the outer ring, or phenolic iodine, of T_4, shows a greater preference for T_4 than reverse triiodothyronine (rT_3), and is not inhibited by propylthiouracil. Both the type I and II deiodinases, however, are stimulated by thiols and inhibited by iopanoic acid; the latter finding is important to the original discovery and clinical investigation of the type II enzyme.

NUTRITION AND THE HYPOTHALAMIC–PITUITARY AXIS

The hypothalamic-pituitary control of TSH secretion is quite different between species. The following comments refer only to humans. Small decrements in the circulating concentrations of T_4 and T_3 in normally fed subjects increase TSH concentrations and augment TSH response to TRH. Therefore, the decline in T_3 that accompanies fasting, dieting, or low-carbohydrate intakes (see below) would be expected to be associated with increased TSH concentrations or an augmented response to TRH. This, however, is not the case. Paradoxically, different studies have reported that unstimulated TSH is decreased (16, 28, 69, 82, 108) or remains unchanged (23, 79), and the TSH response to TRH is unaltered (1, 40, 53, 82) or blunted (4, 16, 17, 21, 23, 69, 108). A partial explanation for this paradox is that pituitary T_3 concentrations are maintained by type II deiodinase using T_4 for the intracellular generation of T_3 (93). Since T_4 concentrations are little changed by fasting, this scenario could explain the lack of response of the hypothalamic-pituitary axis. Unfortunately, this explanation is only partial because it does not account for the paradoxic decline in TSH and response of TRH with caloric restriction or the fact that these responses are not blunted during overnutrition, when circulating concentrations and production of T_3 are increased (34). These observations suggest that overnutrition and un-

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dernutrition alter the sensitivity of the hypothalamic-pituitary feedback system. Indeed, the conclusion that the sensitivity of the hypothalamic-pituitary axis is shifted by overnutrition and undernutrition is supported by the finding that basal and stimulated TSH concentrations are not suppressed during overfeeding when T_3 concentrations are increased but that the addition of small amounts of T_3 effectively suppresses the hypothalamic-pituitary axis (103). The conclusion is also supported by the fact that the administration of small amounts of T_3 during fasting suppresses TSH concentrations and TSH response to TRH stimulation (40, 77). Also of interest in this regard is that fasting induces a shift in the hypothalamic-pituitary response in hypothyroid subjects despite their reduced concentrations of T_4 and T_3 and their elevated basal TSH concentrations (10). The additional observation that the blunted TSH response during starvation can be normalized by administration of iopanoic acid, which inhibits T_4-to-T_3 conversion in the pituitary, suggests that the hypothalamic-pituitary negative feedback system is intact but its sensitivity altered, since the decreased T_4-to-T_3 conversion in the pituitary was properly detected (20).

Other inhibitors of TSH secretion, such as somatostatin, dopamine, and glucocorticoids, could play a role in regulating TSH secretion during starvation. Based on pharmacologic studies, any role of increased dopamine activity is doubtful, since administration of the dopamine antagonist metoclopramide does not reverse the TSH suppression (83, 87). In addition, the fall in TSH due to starvation cannot be reversed by metyrapone administration, rendering unlikely any glucocorticoid mediation of the starvation-induced TSH suppression. Somatostatin, however, could be involved in altering the hypothalamic-pituitary sensitivity. In humans, one could postulate that the fall in serum glucose during fasting and the concomitant initial increase in serum growth hormone levels might sufficiently stimulate somatostatin secretion, which is responsible for the decrease in serum TSH levels (3, 6, 92, 106, 111, 112). This postulate is supported by the observation that feeding small amounts of glucose to fasted subjects prevents the expected blunting of the TSH response to TRH in humans (84). Glucose in vitro has also been shown to stimulate both the type I and type II deiodinases (44) which provides another explanation of this effect. Therefore, whether or not the blunted sensitivity of the hypothalamic-pituitary response during starvation is mediated through somatostatin is still unknown. Other neuroendocrine factors could also play additional roles in this adaptive response, including the monoamine neurotransmitters and other peptides. For example, strong evidence suggests that alpha-adrenergic stimulation positively influences TSH release in the rat by stimulating TRH release (2). Caloric restriction might be expected to interrupt this effect. Serotonin also has a positive influence on the release of TSH in the rat (62). Tryptophan, the serotonin precursor, has a negative

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influence on hypothalamic TRH release, however (72). An interesting possibility is whether the well-recognized effects of food intake, particularly carbohydrate, on the CNS concentrations of serotonin and tryptophan play a role. Whatever the nutritional effects on the hypothalamic-pituitary axis, the mechanism(s) of this adaptive response is probably indirect and presumably results from the effects of neuroendocrine factors that modulate the positive influence of TRH on TSH secretion.

THE THYROID GLAND

The best known nutritional factor involved in thyroid function is iodine. The thyroid gland is the only organ of the body that requires iodine for normal function. The thyroid gland, salivary glands, gastric mucosa, and choroid plexes of the brain can secrete iodide against a gradient, but thyroid cells are the only cells that can incorporate into organic compounds and store iodide in the body. Iodide is cleared from the body primarily in the urine. The renal clearance rate is 30–50 cc/min and is little affected by iodide intake.

The thyroid cells actively transport iodide from the plasma. This process is regulated by TSH, presumably through a cAMP-dependent process. The iodide in the thyroid is then rapidly oxidized and bound to tyrosyl residues in thyroglobulin, a reaction that requires an enzyme peroxidase and H_20_2. Subsequently, the monoiodotyrosine and diiodotyrosine formed are "coupled" to form T_3 and T_4.

Secretion of thyroid hormones from the thyroid gland is regulated by TSH through a cAMP-responsive process. This response is not rapid but takes 1–2 hours for T_3 levels and longer for T_4 levels to rise in the plasma. Secretion is a complicated process of cellular endocytosis of the stored thyroglobulin from the colloid of the gland. These phagosomes are then transported from the apical side of the thyroid cell. Following digestion of the thyroglobulin, T_4 and T_3 are secreted into the capillaries surrounding the thyroid cell base. Uncoupled monoiodotyrosine and diiodotyrosine are deiodinated and the iodide recycled for new hormone synthesis.

NUTRITION AND THE THYROID GLAND

The optimal daily iodide intake is well established as between 100 and 200 μg/day. This amount is required to abolish goiters in geographic regions where endemic goiters due to iodide deficiency exist. A daily supply of 150 μg iodide is considered adequate. The thyroid gland can adapt to wide fluctuations in iodine intake, however, as the thyroidal clearance of iodide can vary from 5 to 100 cc/min. The amount of iodine in foods in different regions of the world varies widely, however. Therefore, until iodine was added

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commercially to the salt supply, iodine intake was, and in some regions is still, quite variable. It has become obvious that an adequate iodine supply can be assured only if the salt used in households as well as in the food industry is sufficiently iodinated. In many countries, particularly in Europe, salt iodination is not mandatory; thus, half of the population has moderate to severe iodine deficiency. Recently, the iodization of salt has been carefully evaluated, and unexpected variations in some commercially available salts have been discovered. In particular, iodine (I_2) in "iodinated" salt preparations tends to evaporate with storage. In properly iodinated preparations, however, the iodide content remains constant. In the United States this goal seems to be adequately achieved.

Adverse effects have accompanied the increased ingestion of iodine in iodide-deficient areas. These effects occur because multiple nodular TSH-independent (autonomous) goiters are common in endemic areas that predispose the local population to the development of hyperthyroidism when the iodide supply is abruptly increased. This problem does not arise if adequate iodide is supplied early in life and before the development of goiter. Other adverse effects of altering (increasing) iodide supply have been reported. The occurrence of autoimmune thyroiditis appears to be increased, although the mechanism has not been elucidated. Also, in countries such as Japan, where very large amounts of iodide are ingested with seaweed intake, there is a higher incidence of hyperthyroidism and hypothyroidism that is corrected when the iodide intake is normalized.

Between 1960 and 1975, the iodide intake in the United States increased dramatically. In Chicago, for example, the increase was 3–5-fold. Much of this additional iodide in the food chain came from the use of iodide as a bread conditioner, in sterilizing agents used in the milk industry, and in medications, including the greater use of iodinated roentgenographic contrast media. Table salt contains less than 0.01% iodide, whereas someone receiving potassium iodide as an expectorant might ingest several grams of iodide daily. One consequence of this increased intake was the lower long-term response rate to medical treatment of patients with Graves' disease (110). Recently, however, this rate has improved coincident with a decrease in the intake of iodide in the United States (95). The decline in iodine in the United States diet is consistent with the use of non-iodine-containing bread conditioners in the baking industry. Except for iodide metabolism, the effects of other nutritional elements on the thyroid gland have been poorly studied.

The thyroid gland receives a rich autonomic nervous system innervation. Secretion can be increased directly by alpha- and beta-adrenergic agents (68). In view of the modulation of the hypothalamic-pituitary axis by adrenergic influences and their dietary manipulation, nutritionally induced adrenergic influences may well alter intracellular and glandular secretory processes as well. Starvation is accompanied by decreased sympathetic nervous system

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activity and overnutrition by increased activity (31). Most likely, therefore, a portion of the eventual decrease in T_3 and T_4 with starvation and their increase with overnutrition is caused by direct influences of the autonomic nervous system, particularly the sympathetic nervous system, on glandular secretion. A possible role at this level for dietary carbohydrate, because of its important modulating effect on the sympathetic nervous system, appears likely but remains unknown (33).

PERIPHERAL THYROID HORMONE METABOLISM

Thyroxine is the major secretory product of the thyroid gland (Figure 1). Under normal nutritional conditions and energy balance, only a small amount of T_3 is secreted from the thyroid gland. The remainder is formed through monodeiodination of the outer ring of T_4 by the peripheral, or type I,

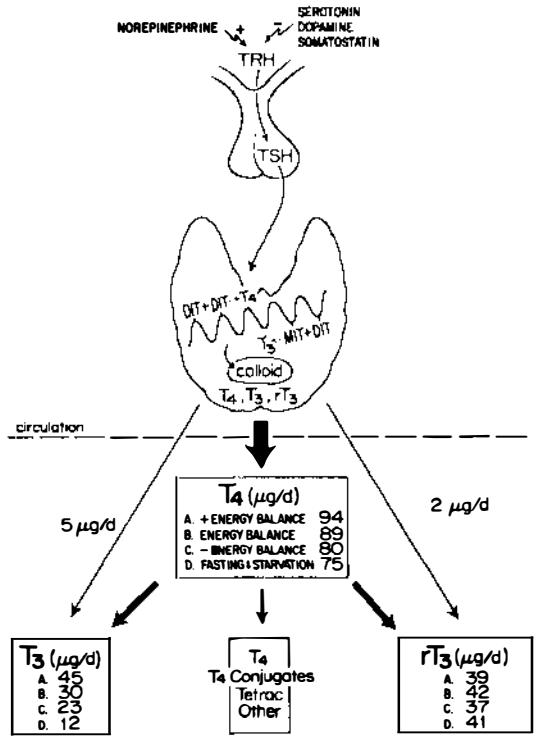

Figure 1 depicts the physiologic relationships among the CNS, pituitary, and thyroid gland and the well-recognized effects of overnutrition and undernutrition (dieting) and fasting on the peripheral daily production rates of thyroxine (T_4), triiodothyronine (T_3), and reverse triiodothyronine (rT_3). Values are from our laboratories or best estimates from the literature. DIT = diiodotyrosine; MIT = monoiodotyrosine; TRH = thyroid releasing hormone; TSH = thyroid stimulating hormone.

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5'-deiodinase. This enzyme is modulated by nutrition and other intermediary metabolic factors. The thyroid gland therefore produces 10 times more T_4 than T_3, but T_3 accounts for most, if not all, of the biologic activity. This data has led some authors to refer to T_4 as a "prohormone."

Once in the plasma compartment, T_4 is bound to three thyroid-binding proteins that are synthesized in the liver. These proteins include thyroxin-binding globulin (TBG), which binds two thirds of the T_4 in the circulation with high affinity. The remaining hormone is bound with low affinity to thyroxin-binding prealbumin (TBPA) and albumin. The T_3 binds to TBG with lower affinity than T_4 as well as to the other thyroid-binding proteins. Both hormones are predominantly protein bound. Only 0.03% T_4 and 0.3% T_3 are unbound, or "free," as determined by equilibrium dialysis. Although both are predominantly bound to thyroid-binding proteins, the 10-fold higher free fraction of T_3 compared with T_4 accounts for the much larger distribution volume of T_3 (30 liters) than T_4 (10 liters). Kinetic analysis has shown that most of the extrathyroidal T_4 is in the plasma, liver, and kidneys, and only small amounts are in other tissues, mainly muscle, brain, and skin. The distribution of T_3 is quite different. Only one fourth of the T_3 is in plasma. There is a small amount in liver, and three fourths of the T_3 is in the slowly equilibrating tissues, including muscle, brain, and skin.

Clinically, levels of the free and not the total circulating hormones correlate best with the negative feedback control of the hypothalamic-pituitary-thyroid axis. This correlation led to the assumption that only free hormones were available for entry into cells for their thyromimetic effects. This concept is now being challenged, however. The amount of hormone degraded is estimated to be well in excess of the free hormone available for cell entry. Therefore, to make up the known amounts of hormone produced and degraded each day, free hormones must become available by dissociation from the low-affinity thyroid-binding proteins. One explanation of how the free hormone concentrations provide an appropriate clinical measurement of thyroid status is the existence of a direct relationship between free hormone and hormone bound to low-affinity binding sites on TBPA and albumin and a reciprocal relationship with "empty" high-affinity binding sites on TBG. This hypothesis has stimulated studies of the tissue uptake of thyroid hormones and whether blood flow to organs, cellular-associated binding proteins, and active transport processes might alter tissue uptake of thyroid hormones, their metabolism, or their action.

NUTRITION AND PERIPHERAL THYROID HORMONE METABOLISM

The two types of deiodinases that can convert T_4 to T_3 have already been discussed in relation to the control of TSH secretion. Interestingly, the

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deiodinase type II, which is found in the CNS and brown adipose tissue, can be stimulated in the latter tissue by alpha-1-agonists (70). Since insulin-mediated glucose metabolism in insulin-sensitive areas of the brain activates the sympathetic nervous system, the type II deiodinase might be modulated in this manner by nutritional factors as well. The main regulators, however, are T_4 and rT_3, which are potent inhibitors of this enzyme. The CNS contains another deiodinase, the type III deiodinase, which removes only the inner-ring iodine. The type III enzyme is also found in skin and placental tissues. No effect of nutrition on this enzyme has yet been reported. Whether or not this enzyme is responsible for all of rT_3 production is not certain (the type I enzyme may also have inner-ring deiodinating activity), but rT_3 production is known to be unaffected by nutrition. The commonly recognized nutrition-related changes in rT_3 concentration are due to changes in its rate of degradation.

The type I deiodinase of the liver is likely to be the main source of circulating T_3. The enzyme is decreased in hypothyroidism and its synthesis is stimulated by thyroid hormones. The other important regulating factor is nutrition, particularly the amount and composition of the energy supplied and the energy balance state of the individual (104). For example, during starvation, plasma concentrations of the enzyme decline and production rates decrease by half or more (81, 99, 105). Type I and II deiodinases are therefore separately regulated, which ensures differences in tissue concentrations of T_3, particularly in the brain compared with the rest of the organism. This difference has led to the concept of selective organ and tissue specificity for thyroid hormones.

As mentioned above, rT_3 concentrations increase during starvation without a change in rT_3 production. This dichotomy is the consequence of the decreased disposal of rT_3 due to the deactivation of the deiodinase responsible for the further metabolic disposal of rT_3. These changes are mimicked by substituting fat for carbohydrate in the diet, but the decline in T_3 is less with carbohydrate restriction than with starvation. Therefore, the activity of the type I deiodinase is unlikely to depend wholly on the carbohydrate content of the diet. In the absence of carbohydrate, however, the substrate and hormone profile mimics the starved condition, including the development of ketosis. This result has led to the suggestion that the altered redox state characteristic of starvation and carbohydrate restriction might be a major factor regulating the activity of the peripheral type I deiodinase. Furthermore, hypocaloric dieting, regardless of dietary composition, produces a change in the circulating concentrations of thyroid hormones similar in direction, although not in degree, to those observed during total fasting.

With short-term fasting or dieting, T_4 concentrations change very little (1, 17, 47, 69, 74, 82, 88, 90, 104, 107, 109). Free T_4 levels may rise transiently secondary to the inhibitory effects of the high plasma free fatty acid con-

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centrations on plasma protein binding (97). With prolonged fasting, however, T_4 concentration declines in concert with the fall in thyroid-binding proteins (88, 98) and later in response to CNS changes and other thyroidal factors, including eventual iodide deficiency. Studies of the peripheral plasma kinetics of T_4 during fasting are generally in agreement. The T_4 production rate is unchanged or falls slightly over the short periods of starvation studied to date (Figure 2) (81, 99, 105).

Triiodothyronine (4, 17, 21, 23, 26, 28, 69, 79, 82) and free T_3 (4, 17, 21, 23, 98) concentrations decrease during fasting and caloric restriction (57, 74) particularly when carbohdydrate is restricted (74). This decrease is rapid (within 24 hours), usually reaches values 40–50% below normal within three days, and then increases slightly but remains below normal for the duration of the diet or fast. Reverse T_3 concentrations increase during fasting (4, 17, 21, 23, 38, 79, 82, 90, 104) as do free rT_3 concentrations (17, 21) but return to normal within 2 weeks in spite of continued fasting. As noted, studies of the peripheral kinetics of T_3 and rT_3 have confirmed that T_3 production rates decrease during starvation and that the transient rise in rT_3 concentrations during starvation is due to its decreased clearance rate. The primary effect of starvation, therefore, is on the type I outer-ring deiodinase and not on inner-ring deiodination. Overfeeding produces changes in circulating con-

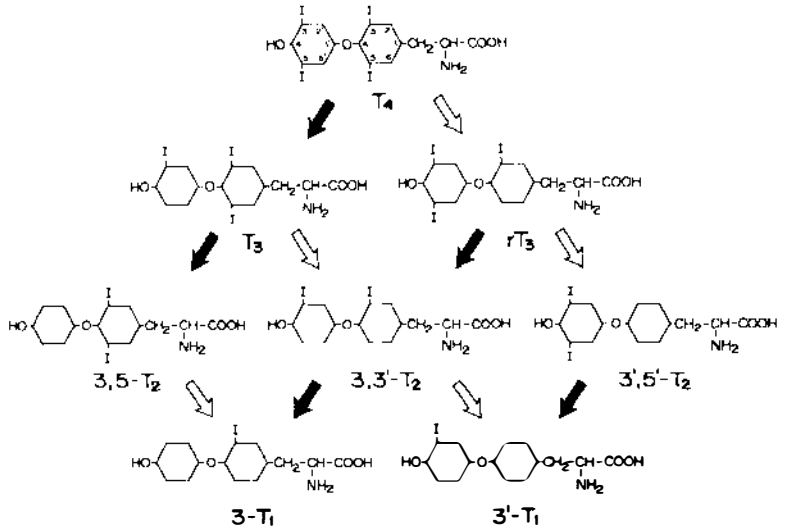

Figure 2 depicts the peripheral monodeiodination cascade. It emphasizes *(dark arrows)* the important peripheral outer-ring type I deiodinative production of T_3 from T_4 and disposal of rT_3 to 3,3'-T_2. Nutritionally induced alterations in the activity of this enzyme account for differences in the peripheral concentrations and kinetics of T_3 and rT_3. The production and disposal rates of the other iodothyronines in response to overnutrition and undernutrition have recently been published (15).

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centrations and production rates of T_3 opposed to those of fasting. Studies of overfeeding and refeeding again emphasize that in addition to energy intake the carbohydrate content of the diet is an important factor in these nutritional changes.

Dietary Composition

Several studies have dealt with the changes in the concentration of serum T_3 and rT_3 during caloric restriction (8, 9, 14, 27, 42, 43, 45, 48, 55, 58, 60, 74, 78, 91, 96, 102, 113). In these studies the addition of small amounts of carbohydrate did not usually affect the decreased total or free T_3 concentrations yet had a marked effect on rT_3 serum levels. The addition of 36 g of carbohydrate to a 530-kcal diet prevented the increase of rT_3 typical of underfeeding. Similar findings have been reported with larger additions of carbohydrate to low-calorie diets. As serum rT_3 levels are a function of its degradation rate, which is markedly affected by the activity of type I deiodinase, rT_3 concentrations can be considered a sensitive index of type I deiodinase activity. This idea recently has been documented by a kinetic study of rT_3 metabolism in subjects taking 1200- or 3600-kcal diets. Total disposal did not change, yet outer-ring deiodination of rT_3 more than doubled, while the fraction metabolized by alternative pathways decreased (Figure 3).

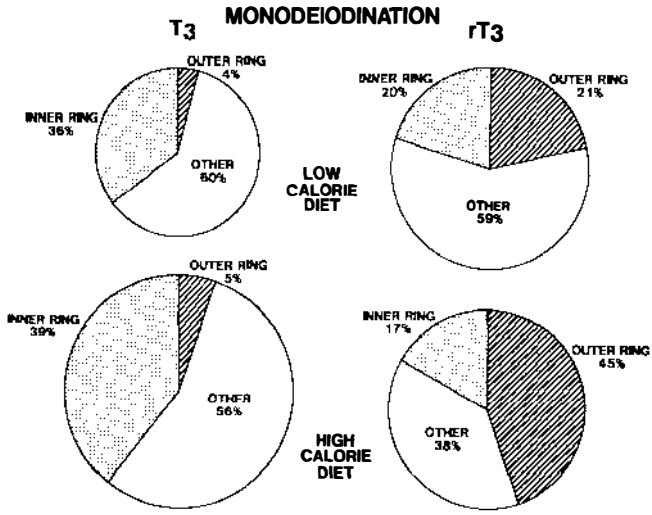

Figure 3 depicts the plasma disposal by monodeiodination and other pathways of T_3 and rT_3 during low- (1200 kcal/d) and high- (3600 kcal/d) calorie diet taken over 20 days. T_3 disposal increased with the high-calorie diet by more than 50%, as depicted by the increased size of the circle, without a change in the fraction of T_3 disposed of by inner- or outer-ring deiodination. The total disposal of rT_3 was unchanged, yet outer-ring 5'-deiodination more than doubled, while the fraction metabolized by alternative (nondeiodinating) pathways was proportionately decreased.

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During undernutrition there are also changes in the concentrations of transport proteins of thyroid hormones. Thyroid-binding prealbumin levels decreased on an 830-kcal/day diet with or without addition of carbohydrates. Thyroid-binding globulin levels decreased in the no-carbohydrate diet, while albumin concentrations were unchanged by either diet. Of importance is that free T_3 concentrations fell in both diets to the same low concentrations, thus raising the question of the level at which carbohydrate intake becomes important in regulating the plasma changes in T_3 and rT_3 levels. The result also clearly indicates that total calories are more important than carbohydrate in these adaptations. Since the decrease in free T_3 was the same whether or not carbohydrate was contained in the diet, the greater decrease in total T_3 in the carbohydrate-restricted diet could be explained by the lowering effect of dietary carbohydrate on the circulating thyroid-binding proteins. Concentrations of TBG and TBPA are increased by carbohydrate overfeeding (113). The effect of carbohydrate on thyroid-binding proteins is also independent of the caloric intake, since TBPA level is increased when eucaloric carbohydrate-restricted diets are fed to normal volunteers (60). Therefore, the synthesis and secretion of thyroid-binding proteins in the liver are clearly affected by dietary carbohydrate. This important function of dietary carbohydrate must be considered when evaluating changes in the circulating concentrations of the thyroid hormones.

The impact of altering dietary composition on thyroid hormones has been investigated in eucaloric diets (Figure 4). In one study (34), fasting-induced changes in concentrations of T_3 and rT_3 were mimicked when carbohydrate was completely eliminated. In another study (35), circulating concentrations of T_3 fell the lowest and rT_3 rose the highest following a 5-day diet containing 105 g of carbohydrate compared with 200 or 420 g of carbohydrate. In a 2-week diet, substituting 315 g but not 92 g of carbohydrate for fat prevented the decrease in T_3 and increase in rT_3 concentrations (91). In another study (78), the addition of 200 g of carbohydrate or protein blunted but failed to prevent completely the decrease in T_3 or increase in rT_3 concentrations in response to 1500 kcal. Free T_3 concentrations were not measured in these studies, and in only two of the four studies was an estimate of thyroid hormone binding performed. Therefore, one must wonder how much of the change in thyroid hormone concentrations was due to altered peripheral metabolism vs that due to changes in thyroid-binding proteins.

The impact of carbohydrate on overfeeding-induced changes in concentrations of T_3 and rT_3 has been the subject of two studies. In one study (35), overfeeding was at two levels of carbohydrate, 204 and 408 g, and weight maintenance was at three levels of carbohydrate. In this study, calories were considered of greater importance for the T_3 changes during overfeeding and weight maintenance, provided at least 200 g of carbohydrates was included in the diet. In an earlier study of longer duration, however, changing

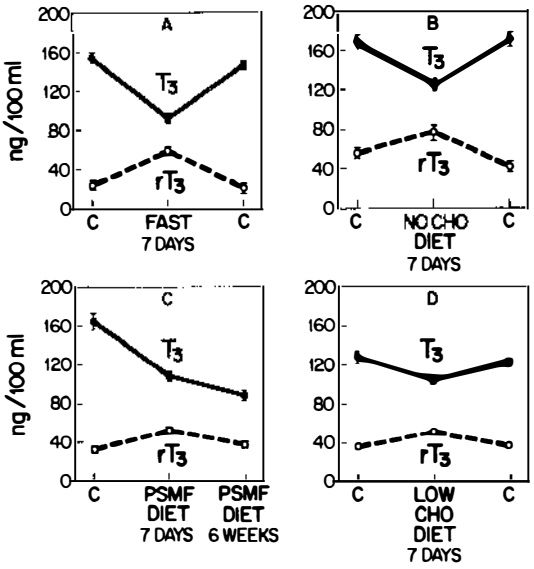

Figure 4 compares the changes in serum concentrations of T_3 and rT_3 induced by fasting (*A*), feeding a carbohydrate (CHO)-free, weight-maintaining diet (*B*), protein-supplemented modified fast (PSMF) (*C*), and low-carbohydrate (10%), weight-maintaining diet (*D*).

the carbohydrate in the diet from 200 to 550 g during weight maintenance produced an increase in T_3 concentration. After long-term overfeeding and a significant gain in weight, however, the same maintenance diets no longer caused these changes (34). This adaptation was suspected to be the result of the increased caloric requirement for maintaining weight after the long-term overfeeding experiment. Therefore, total calories appear to be the predominant factor in determining diet-induced changes in thyroid hormones, provided sufficient carbohydrate is supplied. These studies emphasize the complicated interrelationship between calories, caloric composition, and possibly even energy balance (see next section). In light of these studies and recent studies in rats, one area of interest would be to investigate the impact of carbohydrate on the peripheral kinetics of the thyroid hormones in humans to determine the relative importance of total calories versus carbohydrate on T_3 and rT_3 production rates. One conclusion, in accord with investigations in rats, is that carbohydrate may be required for the induction of the type I deiodinase in liver, and calories or protein may regulate the activity of this enzyme.

Energy Balance

We have reviewed evidence that the peripheral metabolism of T_4 is adjusted to energy intake and/or energy composition. Fasting, undereating, and over-

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eating are clear examples of energy imbalances in which T_4-to-T_3 conversion rates are different. Energy balance can be maintained at many levels of intake and expenditure, however.

We now have evidence that peripheral thyroid metabolism is altered only when there is an energy imbalance, with either an energy surfeit or deficit (Figure 5). The magnitude of this change is roughly parallel with the magnitude of the energy imbalance. In one study (80), two groups of obese subjects were given the same restricted diet. One group also exercised to increase their energy deficit. Free T_3 concentrations decreased as expected in both groups but by a greater magnitude in the exercise group. The decline in resting metabolic rate was also greater in the group with the largest energy deficit, which suggests a potential link between the fall in T_3 concentration and the decline in resting metabolic rate. Such a link seems unlikely, however, since in another study (116) when a compensatory increase in physical activity was added to overfeeding to maintain energy balance, no increase in T_3 concentrations occurred, whereas with overfeeding and no compensatory increase in daily physical activity (a situation producing a positive energy balance), T_3 concentrations increased. In both instances, however, resting metabolic rate increased. We have also observed that the decline in T_3 concentration is the same whether the energy deficit is created by caloric restriction or exercise. Therefore, evidence suggests that peripheral thyroid metabolism is altered when energy intake and expenditure are mismatched (positive or negative

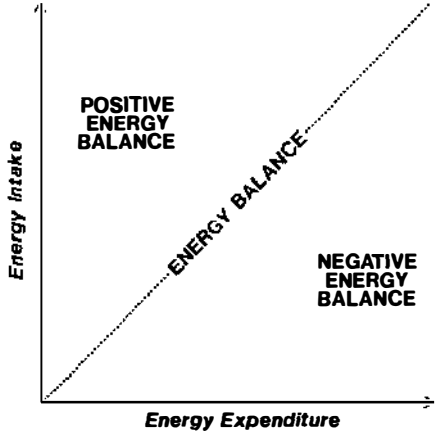

Figure 5 depicts the line of energy balance, which varies with energy intake *(vertical axis)* and energy expenditure *(horizontal axis)*. Recent evidence indicates that peripheral thyroid hormone metabolism is altered when energy intake and energy expenditure are mismatched, which produces positive (above-the-line) or negative (below-the-line) energy balances, while it is unaltered if energy intake and energy expenditure are matched and the subject is in energy balance.

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energy balance) and is unaltered when energy balance is maintained, regardless of energy intake or expenditure. These studies have uncoupled the nutrition-induced alterations in thyroid metabolism from the changes in resting metabolic rate and strongly suggest that other factors, particularly the sympathetic nervous system or other factors regulating substrate fluxes, are responsible for the changes in resting metabolic rate associated with conditions of positive or negative energy balance (Figure 6).

The changes in peripheral thyroid hormone metabolism in response to overfeeding and underfeeding are similar in lean and obese subjects (59, 63). In one report (30), however, free T_3 concentrations were inversely correlated with obesity in inpatient subjects maintained in energy balance. This observation was also confirmed in a second study (59). One large outpatient study has also found T_3 concentrations to be lower in obese than lean subjects. In view of the unique sensitivity of free T_3 to energy balance, however, determining whether there are small differences in T_3 or in its response to caloric challenges between lean and obese subjects will be difficult. In the only report to date comparing the kinetics of T_3 in lean and obese subjects, the clearance and

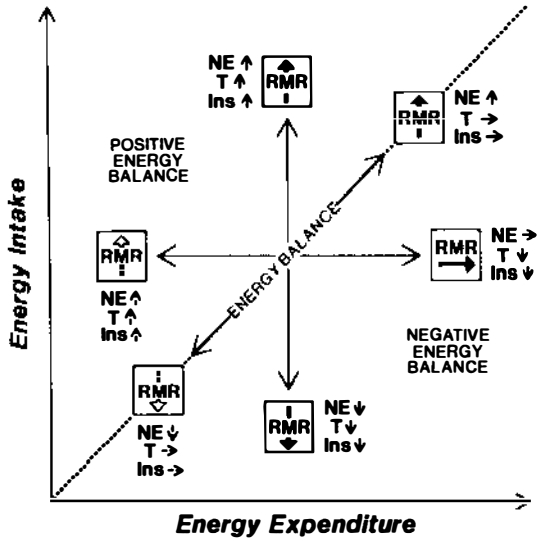

Figure 6 depicts the resting metabolic rate (RMR) as it is altered by conditions of energy balance and imbalance. *Solid arrows* represent definitive results, while *dashed arrows* represent expected or hypothetical results. NE refers to norepinephrine plasma concentrations or appearance rates. T refers to concentration of free T_3, and INS indicates plasma insulin concentrations. An important observation is the concordance of indicators of NE activity with energy flux and thyroid hormone metabolism with change in energy balance. Of further interest is the dissociation of the RMR from thyroid hormone status.

appearance rates of T_3 were similar, but the dynamic changes to overfeeding might be blunted in the obese (30).

CELLULAR THYROID HORMONE METABOLISM AND NUTRITIONAL INTERACTIONS

The mechanism(s) by which thyroid hormones enter into cells and tissues is an active area of research. Several mechanisms have been considered including membrane transport, capillary transit time, and dissociation rates of intercellular and intracellular binding proteins (39). There is good evidence for a low-capacity, high-affinity active transport system in the plasma membrane that depends on cytoplasmic concentrations of ATP (61).

Here again nutrition plays a role, as depletion of glucose in hepatocytes is associated with an intracellular decrease of ATP. Results of liver-perfusion experiments have corroborated these findings and have shown that uptake of T_4, T_3, and rT_3 is limited in livers of starved rats (54, 56). In humans, recent kinetic studies strongly support the idea that the decreased T_3 production resulting from low-calorie diets (240 kcal/day) is in part the consequence of a decreased uptake of T_4 by the liver (51). Another possibility is for a stereospecific, energy-dependent transport system responsible for accumulating T_3 against a gradient in the nucleus of the cell (75). The concept that free hormone is the only hormone available to the cell has been challenged. Circulating nondialyzable factors that inhibit protein binding in pathologic conditions have been described, and free fatty acids bound to albumin have also been postulated to alter cellular hormone availability. Whatever the case, the mechanism for cellular uptake of thyroid hormones is still to be elucidated.

Although there is evidence for extranuclear sites of thyroid hormone action, such as binding to and direct stimulation of mitochondrial oxidative metabolism, stimulation of glucose and amino acid transport, and red blood cell calcium transport, the most convincing evidence is that thyroid hormones act primarily by binding and occupying low-capacity, high-affinity nuclear receptors in thyroid-sensitive tissues, with generation of mRNA products of genes regulated by T_3 (76). Specific tissues and functions that are well studied include an increase in growth hormone mRNA from rat pituitary cells, suppression of TSH-beta mRNA in mouse pituitaries, and others. Figure 7 depicts an overview of thyroid hormone cellular actions.

One problem relating to the discovery of how thyroid hormones regulate genetic expression can be understood from the work of Oppenheimer and co-workers (76). They have discovered that T_3 amplifies the stimulatory effect of carbohydrate on fatty acid synthesis and transcription of several key enzymes in rat liver. One such enzyme is the cytosolic malic enzyme. Other

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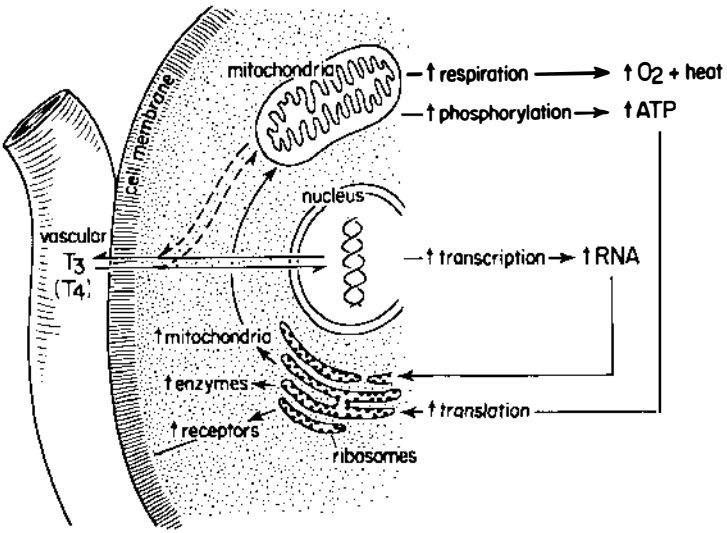

Figure 7 is a schematic depiction of thyroid hormone cellular actions. See text for details.

proteins are also induced by T_3. One, referred to as "spot 14" because of its electrophoretic mobility, is rapidly stimulated by T_3 and is thought to represent an important enzyme for fatty acid synthesis. The conclusion is that T_3 stimulates lipogenesis, not only as permissive hormone, but as a primary inducer of critical enzyme proteins involved in lipogenesis. Carbohydrate metabolism is also influenced by thyroid hormones (71, 100). In these studies thyroid hormones were found to affect key enzymes regulating gluconeogenesis in the liver. For example, the gene for phosphoenol pyruvate kinase, which is stimulated by glucagon-dependent cAMP, is also dependent on T_3. In starvation the activity of this enzyme is increased, favoring hepatic gluconeogenesis from lactate and amino acids. T_3 availability is presumably reduced during starvation, but its requirement seems essential to the transcription of the gene for this enzyme, while glucocorticoids are necessary as modifiers of posttranscriptional events. T_3 also plays an important role in the adaptation from starvation to refeeding. Glucokinase is a key enzyme for glucose storage and utilization. Refeeding with a carbohydrate-rich diet rapidly stimulates glucokinase mRNA. T_3, which increases with refeeding, particularly of a high-carbohydrate diet, is a strong amplifier of the expression of this gene. Again, glucocorticoids act by stabilizing the mRNA of glucokinase. Thyroid hormones are therefore important components of the metabolic adaptations associated with changes in food intake along with the alterations in insulin, glucagon, and catecholamines. The physiologic relevance of these

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studies in primary cultures of rat hepatocytes can be questioned. In recent studies, however, lipogenesis and gluconeogenesis were both increased in human volunteers receiving slightly high replacement doses of T_4, thus supporting the contention that T_3 is an important hormone in the control of both lipid and carbohydrate metabolism (73).

PHYSIOLOGIC IMPLICATIONS OF NUTRITION-INDUCED CHANGES IN THYROID HORMONE METABOLISM

The physiologic significance of nutritionally directed changes in peripheral thyroid hormone metabolism and adaptations in the central nervous system are unclear. One tempting speculation is that the decreased peripheral production of T_3 during fasting and dieting and the increased production during overfeeding contribute to a well-orchestrated hormonal response. The prominent role afforded carbohydrate in this speculation is particularly intriguing, since as an energy source, the carbohydrate content of the diet is the major signal of the fed versus the fasted condition.

As yet there is no unifying physiologic or biochemical explanation of how thyroid hormones function to maintain cellular homeostasis. As more is understood about the cellular mechanisms of thyroid hormone action, the involvement of major tissue specificity in the actions of thyroid hormones has become clear. In the pituitary, thyroid hormone regulates the synthesis of growth hormone. In brown adipose tissue, it regulates the synthesis of thermogenin, the mitochondrial uncoupling protein important to thermogenesis of brown adipose tissue, and in liver it regulates the synthesis of the lipogenic and gluconeogenic machinery. Also clear now is that some tissues, such as the CNS, pituitary, and brown adipose tissue, which contain the type II deiodinase, are not wholly dependent on the T_3 produced by the peripheral type I deiodinase. The ability of these tissues to supply their own intracellular T_3 is an important new concept that has led to the idea that tissues unable to do so depend on peripherally generated T_3. This idea implies that the peripheral tissues, mainly liver, kidney, heart, and muscle, are important target tissues of nutritionally induced changes in peripheral thyroid metabolism. While the effect is predominant on these tissues, this concept should not imply that nutrition is unimportant in the adaptations of other thyroid-sensitive tissues. For instance, the sympathetic nervous system plays an important role in activating the type II deiodinase in the brown adipose tissue of cold-exposed rats and presumably in cafeteria-overfed rats as well. Glucose is known to stimulate type I and II deiodinases and to function as a multiplier of the effects of T_3 action at the nuclear level in several tissues through new protein synthesis. Insulin-stimulated glucose metabolism in insulin-sensitive tissues

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of the hypothalamus is known to activate the sympathetic nervous system (33). Therefore, nutrition is important not only in the adaptation of peripheral thyroid hormone metabolism by adapting the supply of T_3 delivered to peripheral tissues, but it might play a role in the specialized tissues containing the type II deiodinase by modifying the sympathetic system.

Energy Expenditure

An important caveat regarding differences between diseases of the thyroid that produce hyperthyroidism and hypothyroidism and the effects of overnutrition and undernutrition on thyroid hormone metabolism must be kept in mind. Although there are physiologic similarities between the hypothyroid state and underfeeding (e.g. decreased metabolism and heart rate) and between the hyperthyroid state and overnutrition (e.g. increased metabolism and heart rate) and changes in thyroid hormones under these conditions, they should not be equated. There are major differences in the adaptation of the sympathetic nervous system caused by these thyroid diseases and those caused by altered nutritional conditions. The sympathetic nervous system, as judged by several parameters, is suppressed in hyperthyroidism and stimulated by overnutrition, while it is unchanged or stimulated in hypothyroidism and suppressed by undernutrition (31).

The synergistic effects of the suppressed peripheral T_3 production and sympathetic nervous system activity during fasting have rendered difficult any determination of the roles of the two systems in the associated decline in metabolic rate. We have found that fasting reduces the metabolic rate in hypothyroid rats and in hypothyroid rats receiving T_3 or T_4 and that the thermogenic effects of thyroid hormones are blunted in starved rats (114). These observations are consistent with the reported decrease in binding capacity of T_3 in hepatic nuclei of rats during fasting (19, 36, 37, 89). Unfortunately, studies in rats cannot be extrapolated to humans, since the rat, when fasted, rapidly develops hypothyroidism, including low levels of TSH, T_4, and T_3, whereas in humans TSH concentrations fall but T_4 concentrations are unchanged or fall only slightly. The observations in rats are of interest since they have reinforced the potential importance of the sympathetic nervous system in the fasting-induced fall in metabolic rate and have raised the issue of whether human starvation might be associated with changes in peripheral thyroid hormone sensitivity. There is limited data in humans on the effect of fasting on binding of T_3 to circulating mononuclear cells. These studies have frequently disagreed (18, 52, 66, 67, 101); the most recent found no effect of fasting on the binding capacity for T_3 or its dissociation constant in circulating mononuclear cells from fasted obese subjects (13). Refeeding after a period of fasting restores the concentrations of T_3 and the metabolic rate to normal in humans, provided carbohydrate is included in the diet (49).

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Two recent studies are of interest in this regard. One (80) found free T_3 concentrations to be lower during dieting if the subjects exercised to create a greater energy deficit. The lower T_3 concentrations correlated with the lower metabolic rates of these subjects. Another study reported that the expected fall in resting metabolic rate and T_3 during an 800-kcal/day diet containing no carbohydrate was reversed by substituting sucrose for fat isocalorically in the diet (49). These observations link energy expenditure tightly to the fasting- and refeeding-induced changes in T_3 concentrations. Alterations in the sympathetic nervous system, however, may be responsible for these changes as well. The latter study introduces the added possibility that carbohydrate may be required or permissive in uncovering the thermogenic effects of thyroid hormones. This possibility is consistent with the recent observations of a synergistic relationship between T_3 administration and carbohydrate feeding in the induction of several hepatic enzymes and that T_3 multiplies carbohydrate-generated metabolic signals at the cellular level.

Evidence that undernutrition induces a hypothyroidlike state is found in a study in which patients with anorexia nervosa, a condition accompanied by decreased caloric intake and low T_3 concentrations, showed delayed achilles reflexes that returned to normal with the administration of T_3 (29). Also, volunteers receiving hypocaloric diets have exhibited prolonged systolic ejection times that return to normal when either T_3 or T_4 are administered.

Assigning responsibility for the changes in metabolic rate that accompany overnutrition and undernutrition has been difficult because of the complicated interrelationship between thyroid hormone actions and sympathetic nervous system activity and the fact that the nutritionally directed changes in these systems are in parallel. From rat studies and our more recent studies in humans, however, the nutritionally directed changes in SNS-activity appear to be critical to these changes in metabolic rate. Thyroid hormones appear to play a more delayed, prolonged, and permissive role.

Growth and Development

In the young organism, thyroid hormones regulate growth and development. Their role in the maintenance of the organs and cells of the fully mature organism is not as clear. They are thought to regulate protein turnover and the concentrations of structural, enzyme, membrane, and organelle proteins of the body. Once an organism has acquired an amount of lean tissue compatible with its genetic and environmental influences, mechanisms come into play that attempt to maintain it. To survive long periods of fasting, lean tissue must be conserved. This role is the one in which fasting-induced alterations in thyroid hormone metabolism might be most important.

There have been several studies of the effects of T_3 and T_4 on nitrogen balance in fasted and caloric-restricted subjects. Unfortunately, only a few of

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these studies have included simultaneous measurement of metabolic rate. In most, nitrogen losses were accelerated and resting oxygen consumption increased when physiologic or superphysiologic amounts of T_4 and/or T_3 were administered (7, 11, 12, 64). There are reports, however, that no additional catabolic effect followed fasting or hypocaloric dieting when T_4 was administered (65, 86) or when small amounts of T_3 were administered to overcome the fall in T_3 associated with a "proteic" reducing diet (85). This result was not the case, however, when T_3 was administered in a similar fashion to fasting subjects; there it reportedly caused increased nitrogen losses (40), increased 3-methyl histidine excretion (22), or increased urea and creatine excretion (25). However, a portion of the excess creatinurea of fasting is obliterated by feeding excess energy in the form of sucrose to thyrotoxic rats (24). These studies lead to the conclusion that either the addition of thyroid hormones in nonphysiologic amounts or replacement of T_3 with amounts that prevent its decrease during complete fasting increases nitrogen losses and impedes the important adaptation that spares lean tissue during fasting. Supplying carbohydrate in the diet ameliorates these catabolic effects, and the addition of extra protein may also prevent it. These observations offer important insights into the design of diets for weight reduction; however, the decreased T_3 that accompanies fasting is clearly an important factor in the adaptation to reduced caloric intake.

There have been few studies of protein turnover and breakdown rates in fasted or dieting subjects. These studies suggest, as one might expect, that there are differences between growing children and adults (46). Protein breakdown rates in adults consuming weight-maintenance or low-energy diets without protein are dramatically decreased (41), but when the hypocaloric diets contained high-quality protein, no change in protein breakdown was found (115). In an important study, protein breakdown rates decreased in obese subjects who were fasted for one week (50). This decrease correlated with decreased levels of free T_3 and, since the other hormones measured were altered in a catabolic direction, the researchers concluded that the fasting-induced decrease in peripheral thyroid metabolism represented an important adaptive phenomenon. Administration of recombinant methionyl human growth hormone to obese subjects receiving a modestly restricted diet prevented nitrogen wasting and concomitantly prevented the expected decline in T_3 levels (94). The decreased T_3, therefore, is not the only factor responsible for preventing the loss of nitrogen during dieting.

SUMMARY

In summary, nutritionally directed alterations in thyroid hormone metabolism appear to be adaptive and to serve important protective roles in the overall

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economy of the body. These adjustments to nutrition are found at practically every level of thyroid regulation, beginning in the CNS and ending with the final action of thyroid hormones in the nucleus of cells. The cellular actions of thyroid hormones modify, and are modified by, as yet poorly understood interrelationships with substrates and other hormones. The level and composition of the energy intake, including whether the organism is in energy balance, are important signals directing these hormonal adaptations.

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