MINI REVIEW

Age-related changes in thyroid hormone action

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Aging is associated with a variety of hormonal changes (1, 2). Most of these changes probably are secondary to the age-related changes in nutritional status, body composition or increased prevalence of certain illnesses (2). Some changes, however, may well have a primary role in the emergence of various phenotypic changes of aging. For example, it has been suggested that the age-related decline in muscle mass may be partially the result of growth hormone deficiency (3). Although the evidence in favor of this conclusion is circumstantial, it provides the conceptual model for the notion that hormonal changes can be pivotal in the aging phenomenon. In this regard, the age-related changes in thyroid hormone physiology have attracted the interest of both the clinicians and basic biologists alike. The similarities between the clinical signs and symptoms of hypothyroidism and the clinical changes seen commonly in the elderly are remarkable (4). In addition, the relative paucity of the clinical signs of adrenergic stimulation, especially in a subset of hyperthyroid elderly patients with apathetic hyperthyroidism (5–7), further suggests that certain biological functions become less responsive to thyroid hormone with age. In this paper we will review the clinical, physiological and biochemical evidence substantiating the insensitivity of certain physiological and biochemical parameters of aging mammals to thyroid hormone and discuss the recent literature pertaining to the molecular basis of the age-related changes in thyroid hormone action.

Clinical and physiological changes

One of the early pieces of evidence in favor of reduced thyroid hormone action with aging was the finding of reduced basal metabolic rate (BMR) in the elderly (8). However, this observation was later found to be independent of thyroid hormone and to be attributed mostly to the age-related decrease in lean body mass (9). Despite negligible changes in plasma thyroid hormone concentrations, elderly subjects often manifest a host of clinical signs and symptoms that are reminiscent of hypothyroidism. These manifestations are summarized in Table 1. Thus, the clinical diagnosis of hypothyroidism in the elderly is, at best, unreliable. Along similar lines, the clinical diagnosis of hyperthyroidism in the elderly also is difficult. With the exception of body weight loss, cardiac arrhythmias and congestive heart failure, most of the classical signs and symptoms of hyperthyroidism, especially those related to adrenergic hyperactivity, sometimes are blunted in older individuals (5–7).

The increased incidence of body weight loss in the hyperthyroid elderly patients can be misinterpreted as an apparent increase in the catabolic effect of thyroid hormone with age. Of interest is that in an animal model of aging where kidney failure and gross tumors were excluded, thyroid hormone administration resulted in a greater degree of body weight loss compared to younger animals (Fig. 1) (10). This difference in body weight loss, however, could be ascribed totally to reduced food intake in aged rats. When differences in food intake were taken into account and young rats pair-fed with aged rats were included as controls, the age-related differences in catabolic effects of thyroid hormone disappeared (10). It is possible that a similar explanation may underlie the increased incidence of body weight loss in elderly hyperthyroid patients. Anorexia is common and may occur in as many as 36% of elderly patients with hyperthyroidism (5).

It is noteworthy that Frolkis et al. (11) found an increased catabolic response to thyroid hormone with age. However, this study did not rigorously control for the age-related differences in food intake and the plasma free T4 concentrations were higher in the older animals.

A confounding variable in the studies in laboratory animals is the difference in the basal metabolic rate of young rats and aged rats. However, it has been shown that short-term dietary restrictions similar to the pair-fed rats (10) lower the BMR of young rats to a level comparable to that of aged rats (12).

The reduced signs of adrenergic hyperactivity in elderly hyperthyroid patients may well be the result of the age-related desensitization of beta adrenergic receptors (13). Although some have questioned the modulatory role of thyroid hormone on beta adrenergic receptor activity of human heart (14), Martin et al. (15) in a series of carefully conducted studies have found that short-term administration of 100 μg of triiodothyronine (T3) per day in healthy volunteers increased the heart rate and contractility of myocardium in response to isoproterenol, a selective β-adrenergic receptor agonist. This study clearly shows the role of T3 in enhancing myocardial sensitivity to catecholamines. Similar studies in the elderly may not be feasible for ethical reasons. Of note is that the heart rate...
response to catecholamines is reduced in the elderly regardless of thyroid function (16). Whether the changes in thyroid hormone action with age has any role in the age-related decline in β-adrenergic receptor sensitivity remains to be shown.

The higher incidence of cardiac arrhythmias and congestive heart failure in the elderly hyperthyroid subjects is most likely related to the increased prevalence of organic heart disease in the elderly (5). There is still no convincing evidence that myocardial sensitivity to thyroid hormones is increased with age. The available data suggest a reduction in thyroid hormone action on the cardiac tissue of aging animals (see next section).

One parameter of thyroid hormone sensitivity that is easy to assess in humans is the effect of the hormone on pituitary TSH secretion. In a cross-sectional study of euthyroid subjects, the slope of the curve correlating free T₄ to sensitive TSH measurements, an index of pituitary TSH secretory set point, was not altered significantly in elderly subjects compared to young subjects (Fig. 2) (17). A more direct estimate of pituitary sensitivity to thyroid hormones is provided in studies whereby TSH secretory response to TRH administration following an exogenous iodide-induced reduction in thyroid hormone concentrations was reduced significantly in the elderly (18). Despite the reduced TSH response to TRH under those experimental conditions, the TSH secretion rate in the elderly subjects is higher compared to younger controls (19). This may, in part, be secondary to an age-related alteration in TSH sensitivity to thyroid hormones.

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Table 1. Clinical features of hypothyroidism found commonly in euthyroid elderly individuals

<table>
<thead>
<tr>
<th>I. Skin and appendages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry, pale and cool skin, decreased sweating, bruising tendency, dry and brittle hair, slow growth of nails</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Cardiovascular system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased cardiac output, decreased heart rate, increased vascular resistance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>III. Constipation, hypochlorhydria, reduced rate of absorption</th>
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</thead>
<tbody>
<tr>
<td>Constipation, hypochlorhydria, reduced rate of absorption</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV. Nervous system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow mentation, slow and clumsy movements, lethargy, decreased hearing, decreased dark adaptation, thick slurred speech, carpal tunnel syndrome, slow relaxation of deep tendon reflexes, cold intolerance</td>
</tr>
</tbody>
</table>

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Fig. 1. The body weight changes (g) in euthyroid (▲), hyperthyroid (T₃-treated, 15 μg/kg ip daily for 10 days, starting on day 20) (●) and hypothyroid (methimazole treated, 0.025% in drinking water for 4 weeks) (■) young rats (6 months old) (A), young rats pair-fed with aged rats (B), intermediate age rats (15 months old) (C) and aged rats (24 months old) (D). Reprinted from Mooradian AD. Exp Gerontol 1990;25:29–35, with the permission of the publisher.
More recently, Lewis et al. (20) found that 2.5% of ambulatory elderly clinic patients have inappropriately normal serum TSH concentrations despite a subnormal free T₄ index. This was attributed to resetting of the thyroid hormone feedback regulation threshold of TSH secretion (20).

Overall, the clinical evidence for reduced thyroid hormone sensitivity with age is, at best, circumstantial. Direct estimates of thyroid hormone sensitivity can be demonstrated more easily in animal models.

Biochemical changes
Thyroid hormone regulates a diverse array of cellular activities. Some of the thyroid hormone response parameters are summarized in Table 2. Thyroid hormone may augment or attenuate the expression of specific genes. The effects of aging on the T₃ responsiveness of these biomarkers of thyroid hormone action are shown in Table 2.

Much of the literature on the effect of aging on thyroid hormone action has been limited to age-related changes in serum hormone concentrations, binding to plasma proteins, thyroidal secretion and peripheral metabolism of thyroid hormones (1, 2, 21–24). The age-related changes in thyroid hormone economy were discussed recently (25) and are summarized in Table 3. It is noteworthy that, unlike earlier studies (21), recent investigations using non-compartmental methods and more accurate purification of the tracers have suggested that the T₄ and T₃ clearance or production rate may not change with age (26, 27). However, the studies in the two age groups were not done in parallel and there was some overlap in the ages of subjects within the older group and the young controls (26, 27). Overall thyroid function is well preserved until advanced age and there is no evidence that alterations in thyroid gland secretions contribute to aging (28).

The effects of age on the biological effects of thyroid hormone have received little attention and the precise biochemical mechanisms involved in these changes remain unknown. Measurements of minimal oxygen consumption under carefully controlled conditions have indicated a significant age-related decline in tissue responsiveness to calorigenic effects of thyroid hormone (29). The studies that have shown an increased response of oxygen consumption to thyroid hormone with age did not control carefully the age-related differences in thyroid hormone sensitivity.

**Fig. 2.** The correlation of the steady-state serum free T₄ concentration with the logarithm (log) of serum TSH value in middle age (<60 years of age, N = 122) (A) and elderly (>60 years of age, N = 259) (B) outpatients. The slope of the curve is an estimate of pituitary sensitivity to thyroid hormones. The calculated slope in middle-aged patients was −0.055 ± 0.008 and in elderly patients was −0.038 ± 0.005. Reprinted from Friedman D, Reed RL, Mooradian AD. Age 1992;15: 9–13, with the permission of the publisher.
Thyroid T3 Parameter chronically reduced inducing hormone (d) (c) (a)

Table 2. The effects of aging on thyroid hormone (T₃) responsiveness of select biomarkers of thyroid hormone action.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>T₃ responsiveness in aging</th>
</tr>
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<tbody>
<tr>
<td>I. Positively regulated</td>
<td></td>
</tr>
<tr>
<td>(a) Metabolic rate</td>
<td>Decreased</td>
</tr>
<tr>
<td>(b) Catabolic effect</td>
<td>No change or increase⁽ᵃ⁾</td>
</tr>
<tr>
<td>(c) Lipid peroxidation</td>
<td>Decreased or no change⁽ᵇ⁾</td>
</tr>
<tr>
<td>(d) Malic enzyme</td>
<td>Decreased</td>
</tr>
<tr>
<td>(e) α-Glycerophosphate dehydrogenase</td>
<td>No change</td>
</tr>
<tr>
<td>(f) Na⁺⁻K⁺-ATPase</td>
<td>Decreased</td>
</tr>
<tr>
<td>(g) Ca²⁺-ATPase</td>
<td>No change in rats</td>
</tr>
<tr>
<td>(h) Sarcoplasmic Ca²⁺-ATPase mRNA</td>
<td>Decreased</td>
</tr>
<tr>
<td>(i) Thymocyte 2-deoxy-glucose transport</td>
<td>Decreased</td>
</tr>
<tr>
<td>(j) Serum angiotensin-converting enzyme</td>
<td>No change</td>
</tr>
<tr>
<td>(k) S₁₄</td>
<td>Decreased</td>
</tr>
<tr>
<td>(l) S₁₄/apo A-I</td>
<td>Altered⁽ᶜ⁾</td>
</tr>
<tr>
<td>(m) α-Myosin heavy chain</td>
<td>Unknown</td>
</tr>
<tr>
<td>(n) GH</td>
<td>Unknown</td>
</tr>
<tr>
<td>II. Negatively regulated</td>
<td></td>
</tr>
<tr>
<td>(a) TSH alpha subunit</td>
<td>Unknown</td>
</tr>
<tr>
<td>(b) TSH beta subunit</td>
<td>Unknown</td>
</tr>
<tr>
<td>(c) Serum TSH</td>
<td>Decreased</td>
</tr>
<tr>
<td>(d) β-Myosin heavy chain</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

⁽ᵃ⁾ If dietary intake is not accounted for.
⁽ᵇ⁾ No down-regulation in hypothyroid aged rats.

Tissue responsiveness to the lipid peroxidation-inducing effects of thyroid hormone also may be reduced if one takes into account the altered caloric consumption of aged rats (31). Thus, the ethane exhalation rate, an index of lipid peroxidation, is reduced in rats with aging. In addition, acutely or chronically T₃-treated aged rats have lower ethane exhalation rates compared to their younger counterparts. When young rats are pair-fed with aged rats, their ethane exhalation rate is reduced at baseline and yet the T₃ responsiveness is enhanced. Thus, the age-related changes in lipid peroxidation rate and its response to T₃ appear to be independent of reduced food intake with aging.

One of the desirable features for a biochemical parameter that would be suitable for evaluation of thyroid hormone action with aging is that it must be modulated closely by thyroid hormones and shows an age-related change at baseline conditions. One such parameter is Na⁺⁻K⁺-ATPase activity. Studies by Gambert et al. (32) have shown that renal cortical Na⁺⁻K⁺-ATPase activity declines modestly with age and the response of this enzyme to T₃ injection is reduced in 20–24-month-old aged rats. Hypothyroid animals did not show the age-related decline in Na⁺⁻K⁺-ATPase activity. A similar trend in age-related changes in hepatic Na⁺⁻K⁺-ATPase activity also was observed (32). As the activity of this enzyme may be partly responsible for the calorigenic effect of thyroid hormone (33), it is possible to attribute the age-related decline in thermogenic effects of thyroid hormone to the changes in Na⁺⁻K⁺-ATPase activity (32). However, data in aging animals should be interpreted with caution because some of the aged rats may have had early renal failure or other diseases.

The response of Ca²⁺-ATPase activity of red blood cell membranes to in vitro thyroid hormone stimulation also is altered with age in humans (34) but not in rats (35). Interspecies differences may explain the discrepancy.

Another T₃ responsive parameter, angiotensin-converting enzyme (ACE), has been used as a biochemical index of thyroid hormone action (36, 37). The unique advantage of this parameter is that assessment of ACE levels does not require invasive techniques because it can be measured in plasma. Carefully conducted studies in animal models of aging have shown that the ACE activity is reduced with age (38). However, this age-related change was independent of reduced caloric intake or altered thyroid state. In addition, there is an inhibitor of ACE activity in serum of rodents (38). This may have been partly responsible for the inability to demonstrate ACE sensitivity to thyroid hormone in rats because this plasma ACE inhibitor activity appears to change with the thyroidal state of the rat (38). This parameter, therefore, is not suitable for studying thyroid hormone responsiveness in aging rats.

The plasma membrane effect of T₃ also is influenced by age. When deoxyglucose uptake by thymocytes in response to T₃ was studied, there was a significant refractoriness to T₃ in older animals. This effect occurred mostly during maturation of the animal and the changes were more pronounced in cells isolated from male rats (39). It is not clear whether this age-related change may partly explain the decreased thymus gland function with age. Of interest is that administration of thyroid

Table 3. Age-related changes in thyroid hormone economy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Changes</th>
</tr>
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<tbody>
<tr>
<td>Radioactive iodine uptake</td>
<td>Decreased</td>
</tr>
<tr>
<td>T₃ Production</td>
<td>Decreased or unaltered</td>
</tr>
<tr>
<td>T₄ Production</td>
<td>Decreased or unaltered</td>
</tr>
<tr>
<td>T₃ Degradation</td>
<td>Decreased or unaltered</td>
</tr>
<tr>
<td>T₄ Degradation</td>
<td>Decreased or unaltered</td>
</tr>
<tr>
<td>Serum T₄ concentration (total or free)</td>
<td>Unaltered</td>
</tr>
<tr>
<td>Serum thyroid hormone binding</td>
<td>Unaltered or decreased</td>
</tr>
<tr>
<td>Serum thyroid hormone binding capacity (T₃ resin uptake)</td>
<td>Unaltered</td>
</tr>
<tr>
<td>Serum TSH</td>
<td>Unaltered or increased</td>
</tr>
<tr>
<td>Circadian TSH Variation</td>
<td>Decreased</td>
</tr>
<tr>
<td>TSH response to TRH</td>
<td>Unaltered or decreased, especially in men</td>
</tr>
<tr>
<td>TSH response to thyroid hormone</td>
<td>Decreased</td>
</tr>
<tr>
<td>Thyroid response to TSH</td>
<td>Decreased or unaltered</td>
</tr>
</tbody>
</table>
hormone to aging animals normalizes some of the parameters of immune competence (40, 41). The studies of Segal and colleagues indicate that the age-related decline in thyroid hormone responsiveness also includes those actions of thyroid hormone that occur at the level of plasma membranes (39).

The effect of age on other extranuclear actions of thyroid hormone, such as actin polymerization (42) or phospholipid-dependent protein kinase activity (43) or bursting of sodium channels (44), is not known. Studies in aging mice have shown that T₃-stimulated EGF (epidermal growth factor) production by the submandibular gland is reduced significantly (45). However, significant sex-related differences could be observed. The response of EGF to dihydrotestosterone was not altered in aging female mice.

One of the cardinal manifestations of the age-related decline in thyroid hormone sensitivity is the reduced cardiac chronotropic effects of thyroid hormones (46). This age-related change could not be attributed to the changes in β-adrenergic receptor number because the thyroid hormone-induced increased in β-adrenergic receptor number does not change with age (47). Thus, post-receptor changes are likely to be responsible for this age-related decline in thyroid hormone-induced β-adrenergic receptor function. This notion is supported by the observation that isoproterenol-stimulated adenylate cyclase activity in hyperthyroid aged rats is only 50% of the level found in hyperthyroid young rats (48). This may partly explain the reduced manifestations of adrenergic overactivity in elderly hyperthyroid patients.

When 12-month-old rats are compared to 2-month-old rats, the hemodynamic consequences of T₃ treatment were attenuated in older rats (46). The decreased sensitivity of chronotropic response to isoproterenol in older rats could be normalized with T₃ treatment. These studies clearly indicated that thyroid hormone-induced and age-related changes in β-adrenergic response are interrelated (46).

The response of the sarcoplasmic reticulum Ca²⁺ ATPase gene expression to thyroid hormone also is reduced in aged rats (49). This may contribute to the age-associated slowing of cardiac relaxation. Another factor known to influence cardiac function, particularly cardiac contractility, is the expression of myosin heavy-chain (MHC) isoforms alpha and beta. Developmental studies show a bimodal pattern of beta isoform expression, with high levels in the neonate that decrease transiently after birth only to increase again with aging (50–52). In contrast, the alpha form decreases steadily following birth (52). These changes can only be related partly to the reduced plasma T₃ levels in aging rats. These studies in general have used very high doses of thyroid hormone and therefore are difficult to relate to the usual physiological changes that occur with age. Effron et al. (53) showed that if senescent rats are treated with T₄ to cause hyperthyroidism, the right ventricular β-MHC is reduced significantly, yet the levels were still higher than that found in the right ventricles of maturing young rats (53). The expression of both genes is controlled by thyroid hormone in an opposite fashion (54, 55). Whereas T₃ increases alpha gene expression, it decreases beta gene activity. In light of studies demonstrating the presence of a negative thyroid hormone-responsive element in the gene encoding the beta isoform, the enhanced expression of the beta MHC with aging and the inability of the hyperthyroid state in aged rats to suppress completely beta MHC transcription (53) would seem to suggest a relative insensitivity of this negative response element to T₃ in aging animals.

The overall protein synthesis and cardiac hypertrophy induced with thyroid hormone also is altered with age. Florini et al. (56) found that although the amount of hypertrophy achieved was not altered with age, older animals had an increased lag time of initiation of cardiac changes following thyroid hormone treatment. The effect of aging on lipogenic enzymes and their response to thyroid hormones and dietary factors has been studied extensively. A number of studies have shown that the steady-state levels of malic enzyme (ME) and α-glycerophosphate dehydrogenase (α-GPD) decline with age (57–60). In addition, there are age-related differences in dietary as well as thyroidal regulation of these enzymes (57–62). However, most of the studies have focused on maturational changes rather than those occurring with senescence. In one study using Sprague-Dawley rats, the level of ME and its response to T₃ and high carbohydrate diet fell between 1 and 6 months, with only minor additional changes noted between 6 and 18 months (59). Based on a hypothetical model linking T₃ action to an intermediate stimulus provided by carbohydrate metabolism, the authors speculated that the mechanism responsible for the age-related reduction in ME activity has two components: a reduction in daily food intake per 100 g body weight and a decrease in hepatocellular responsiveness to carbohydrates (59). However, a direct evaluation of the role of reduced dietary intake in older rats by studying young rats pair-fed with old was not included in this report. A more recent study in male Fischer-344 rats at different ages found that basal hepatic ME activity is reduced with aging (63). Although most of the change was observed during maturation, there was an additional reduction of approximately 50% in ME activity in 26-month-old rats compared to 6-month-old mature rats (63) (Fig. 3). In these studies the animals bearing tumors and those with elevated serum creatinine levels were excluded from the analysis in order to minimize disease-related effects in the aging rats. There was a close correlation between response of ME activity and ME mRNA levels to T₃ in young and aged rat liver (Fig. 3).

Pair feeding of young rats with aged rats resulted in an increase rather than a decrease in basal and T₃-stimulated ME activity (63). This suggests that the age-associated decline in tissue responsiveness to thyroid
hormones was independent of the age-related decrease in food intake. The basal hepatic α-GPD activity also is reduced with maturation, but there were no additional changes with further aging (63). In addition, T₃ responsiveness of α-GPD is no different in aged rats (26 months of age) compared to mature adult rats (63). These studies indicate that hepatic ME is one of the more suitable models for studying age-related changes in thyroid hormone action.

One can argue that the reduced ME response to T₃ in aged rats is secondary to an inherent change in ME gene expression, as evidenced by a 50% decrease in basal levels of expression with age. Several lines of evidence suggest that this is unlikely to account totally for the observed changes with age. First, whereas the basal ME activity decreases by twofold with age, the levels in hyperthyroid aged rats compared to hyperthyroid young rats are fourfold lower (63). Thus, there appears to be a net 50% reduction in T₃-stimulated ME activity with age in addition to the changes in basal levels. It is noteworthy that in younger age groups up to 18 months of age, the response of ME activity to T₃ relative to baseline does not change with age (59). This suggests that mechanisms of reduced T₃ responsiveness associated with maturation are different from those observed in studies of aging animals.

The second line of evidence in favor of reduced ME responsiveness to T₃ with age comes from studies of rats fed 60% fructose diets. This diet resulted in increased ME activity in aged rats to the same level as that of young rats fed identical diets, yet T₃ responsiveness was still 50% reduced compared to T₃-treated young rats fed the same diet (64) (Fig. 4). Similar trends were found in rats fed 60% dextrose diets. Thirdly, the age-related decrease in T₃ responsiveness also is found in the expression of the S₁₄ gene in aged rats. The rat liver S₁₄ gene encodes a small nuclear protein (pI 4.9, Mr 17,010) that is believed to be involved in lipogenesis (65). The basal levels of S₁₄ mRNA were not detectable in neonatal animals but increased steadily with age. In the adult rat, the levels of this mRNA are roughly 200-fold higher relative to the newborn animals. Further aging is associated with even higher levels (66). The S₁₄ gene has served as a valuable marker of thyroid hormone action in the nucleus because of its rapid induction by T₃. In a recent study, thyroid hormone treatment of young euthyroid rats resulted in a 7.6-fold increase in levels of the S₁₄ mRNA, while parallel studies in aged rats (26 months old) yielded a three- to fourfold induction of the gene (67). Although the overall level of S₁₄ mRNA was higher in aged animals, the induction over the euthyroid level was higher in the young as compared to the older animals. This observation is remarkably similar to the 50% reduction in ME response to T₃ with aging. This age-related decline in T₃ responsiveness of S₁₄ is evident in a biochemical parameter that, unlike ME, shows an age-related increase in basal expression. Overall evidence, therefore, favors the notion that T₃ responsiveness of key biomarkers of thyroid hormone action in the liver is reduced with aging.

The changes that we have described for the ME and S₁₄ genes are specific and do not extend to other thyroid hormone-responsive sequences. For example, the expression of the T₃-responsive apolipoprotein A-I (apo A-I) gene product is known to decrease with maturation but the responsiveness to T₃ may not be altered (68). The only difference between the two age
groups is that the expected reduction in apo A-I mRNA observed in young animals during hypothyroidism is not present in the aged group (68). These changes underscore the spectrum of the age-related changes that may occur in response to thyroid hormone.

In the central nervous system (CNS), the expression of pcP-2 gene, a purinergic cell-specific gene, is induced by thyroid hormone during the neonatal development. This thyroid hormone responsiveness is lost in the adult animal (69). These changes were maturational and cannot be extrapolated to the alterations occurring between adulthood and senescence.

Another example of an age-related reduction in the cellular response of the CNS to thyroid hormone is the blunted β-adrenergic receptor upregulation in the synaptosomal membranes of aged rats (24 months old) in response to exogenous T3 administration (70). The adenylyl cyclase activity response to prostaglandin E1 also was reduced in synaptosomal membranes of aged rats. Thyroid hormone did not induce the activity of this enzyme either in young or aged rats (70).

Overall, it appears that aging is associated with altered thyroid hormone effects on several key cellular markers of thyroid hormone action.

Mechanisms of age-related changes in thyroid hormone action

Although thyroid hormone action is mediated through its interaction with various cellular components (35, 42–44), its major site of action is at specific nuclear receptors (65). Age-related changes in biological actions of thyroid hormone are probably the result of various potential changes in hormone delivery to nuclear binding sites, interaction of hormone with its receptors and changes in post-receptor processes modulating gene expression.

The first step in thyroid hormone action is the transport of the hormone to nuclear binding sites. Many investigators believe that serum free T4 and free T3 are more readily available for transport. Studies on the effect of age on thyroid hormone binding to plasma proteins have not shown any age-related changes. The T3 resin uptake in humans does not appear to change with age (71–73), although decreased values have been reported in healthy 60–94-year-old Japanese elderly (74). The immunoreassayable thyroxine-binding globulin (TBG) concentrations also have been reported to be either unaltered (73) or modestly increased (75) with age. Braverman et al. (72) found that the T4 binding capacity of TBG was higher and that of thyroxine-binding prealbumin (transthyretin) lower in older subjects. However, the free T4 concentrations measured by equilibrium dialysis do not change significantly with age (76, 77). The T3 binding capacity of plasma proteins as determined by equilibrium dialysis techniques also is not altered in an aging rat model (78).

It is now generally accepted that cellular transport of thyroid hormone is a carrier-mediated process (78–84). As a variety of carrier-mediated transport processes are
altered with aging (85–90), the cellular uptake of T3 was studied in Fischer-344 rats at 6 and 26 months of age. At steady-state conditions, the total tissue uptake of T3 in the liver, heart and rectus abdominis muscle was reduced in aged rats while T3 uptake by cerebral tissue, femoris and soleus muscles was not altered (78). The subcellular distribution of T3 in the liver was determined and free T3 concentrations in the nucleus, cytoplasm and plasma were estimated. Measurements of free T3 concentration gradients across the cellular and nuclear membranes indicated that the age-related deficit in T3 uptake occurs at the plasma membrane level (78) (Fig. 5). The disproportionate reduction of cellular uptake of levo and dextro enantiomers of T3 indicates that reduced transport capacity of T3 in aged rats is associated with alterations in the stereospecificity of the T3 transport (78). These observations were corroborated with the finding of a reduced liver uptake index (78) and a reduced brain uptake index (90) of T3 in aged rats determined in vivo with the single-injection tissue sampling technique. These age-related changes could not be ascribed to altered tissue binding or metabolism of T3 (78).

The tissue metabolism of thyroid hormone is an important determinant of thyroid hormone action. In general, the deiodination rate of T4 and T3 is reduced in older subjects and the T4 metabolism is diverted to T3 production with age (21, 91). However, the age-related changes often are tissue- and species-specific. In rats, unlike humans, T4 degradation is increased by 50% with age (21, 92). The activity of deiodinase is altered with age in a tissue-specific manner. Decreased hepatic 5'-deiodinase activity has been found in aged rats, while pituitary type II 5'-deiodinase activity is increased (93). The significance of these changes in the age-related alterations of thyroid hormone action remains to be shown.

Other studies in different strains of rats have yielded variable results. In a small study of Long Evans rats, comparing only three young rats with three aged rats, nuclear T3 binding in vivo was no different in the two age groups (24). It is noteworthy that the decreased T3 nuclear binding in vivo has been reported in diabetes (94), food restriction (95, 96) and in states of hyperglucagonemia (97). The decreased cellular uptake of T3 in aged rats may not be a direct consequence of aging, but rather secondary to glucose intolerance, decreased food intake or increased plasma glucagon levels commonly found in aged animals (1, 2).

The interaction of thyroid hormone with nuclear receptors is a major step in thyroid hormone action. In vitro incubation of isolated nuclei with T3 does not favor an age-related change in the affinity or binding capacity of these nuclei to either levo or dextro enantiomers of T3 (78). Other studies, however, have reported some modest changes in T3 receptor affinity with age of donor (98). When nuclear T4 and T3 binding in mononuclear cells of human subjects was studied, the nuclear binding capacity was reduced with the age of the subject and the association constant (Kd) for T4 also increased (and that of T3 decreased) with age (98). There are only a few studies on the effect of age on thyroid receptor isoforms. The ratio of nuclear T3 binding capacity to c-erbA mRNA content is regulated developmentally in a tissue-specific manner (99). In the cerebrum, T3 binding capacity rises in the first 4 days neonatally and thereafter decreases to an adult value. During this time the c-erbA β1-mRNA rises 40-fold while the increase in α1- and α2-mRNA is comparatively modest in the first 10 days of life and decreases to an adult value that is 1.5-fold higher than the fetal level (99). In the liver, the relatively low levels of α1- and α2-mRNA stay constant during maturation while β1- mRNA falls by 60% on day 4. In this tissue, the T3 binding capacity increases sharply to the adult level after day 15 of neonatal life. It appears that there is no direct relationship between mRNA content of various isoforms and T3 binding capacity, suggesting that both translational and post-translational factors are involved in the expression of various T3 receptor isoforms during development (99). These studies should be carried out also in aged animal models in order to differentiate the developmental changes from those related to senescence. Studies of this nature may yield useful information as to the specialized functions for each isoform of thyroid hormone receptor.

The effect of age on post-receptor processes of thyroid hormone action also is not well characterized. Studies on malic enzyme and S14 gene, two biomarkers of thyroid hormone action, indicate that the age-related changes in T3 responsiveness that occur are at the pretranslational level (63, 67). These changes could be related to alterations in transcription factors or could be secondary to structural changes of the gene. An example of the latter is the age-related demethylation of the S14 gene, which would partially explain the increased expression of this gene with age (66). Another
example is the recent suggestion that an upstream region of pcp-2 gene, the PA-2 (−277 to −206), which is responsible for the T3-dependent pcp-2 expression during neonatal life, may be silenced in the adult brain by other elements within the pcp-2 gene without altering the T3-independent expression of pcp-2 in the adult animal (100). Whether these changes persist in the senescent animal beyond adulthood is not known.

More recent work suggests that aging also alters transcription factors involved in S14 gene expression (67). A transcription factor P-1 binds to S14 DNA at nucleotides −310 to −288 and represses S14 gene transcription (101). Another transcription factor, PS-1, binds to S14 DNA at nucleotides −63 to −48 and stimulates S14 gene transcription. Aging is associated with decreased levels of P-1 (67). These changes may contribute to the age-related increase in S14 expression (67). Of interest is the fact that thyroid hormone treatment is associated with increased levels of both the enhancing FS-1 and the repressing P-1 factors (101, 102). Thus, the activity of S14 gene expression in response to T3 is attributed to a net effect of the two factors. The mechanisms underlying the age-related changes in basal S14 gene expression and T3-induced expression appear to be different.

Concluding remarks

Overall, it is evident that aging is associated with resistance to thyroid hormone action, at least in some biological parameters. However, it is not yet clear whether the reported changes represent compensatory events or are manifestations of a generalized resistance to thyroid hormone. The lack of an age-related increase in plasma concentrations of thyroid hormones and TSH, along with a lack of an exaggerated TSH response to TRH, indicate that age-related changes in thyroid hormone action are not similar to those found in generalized thyroid hormone resistance syndromes (103). However, the difference between aging and classical thyroid hormone resistance may be secondary to the changes occurring in the hypothalamic–pituitary unit. Thus, unlike the classical syndromes of thyroid hormone resistance, aging is associated with increased local formation of T3 and an increased number of T3 nuclear receptors of the pituitary (93, 104, 105), along with decreased TRH secretion in the hypothalamus (106, 107). These changes may contribute to the lack of increase in serum TSH and thyroid hormone concentrations, as expected in generalized thyroid hormone resistance. It is likely, therefore, that the age-related thyroid hormone insensitivity is restricted to certain biological systems that may well vary among species.

The literature on the effect of aging on thyroid hormone action is still in its infancy. Many questions remain yet unanswered. The effect of age on various isoforms of thyroid hormone receptors and their interaction with auxiliary proteins has not been addressed. Studies of this nature would shed light on the specialized functions of these various isoforms. The role of dietary changes with age and the carbohydrate intolerance of aging in T3 responsiveness has not been evaluated adequately. Maturational changes should be compared to those seen with senescence. This will provide some insight into the basic processes that modulate development and aging. Finally, from a clinical standpoint, if aging is shown to be truly a state of relative thyroid hormone resistance in key biological systems, and if this is not a compensatory change, one would consider either thyroid hormone therapy or therapy directed at correcting the underlying causes of this “physiological” and possibly tissue-specific hormone resistance syndrome.

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