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Editorial

Tyrosine and the Thyroid Hormones

TYROSINE occupies a crucial place in intermediary metabolism as the precursor of the thyroid hormones, thyroxine and triiodothyronine; of the adrenal medullary hormones, epinephrine and norepinephrine; of the pigment, melanin; and is incorporated into body proteins. (Fig. 1.) It has recently been recognized that in patients with thyroid disorders characteristic changes in the metabolism of tyrosine occur regularly [*1–4*]. The nature and significance of these changes are reviewed here briefly.

In hyperthyroid patients the concentration of tyrosine in plasma is increased nearly 70 per cent above values found in euthyroid subjects [*1,2*]. In addition, after ingesting tyrosine, patients with hyperthyroidism have plasma tyrosine levels which are several times higher than those of euthyroid subjects similarly treated [*3,4*]. Significant increases occur in normal subjects within 5 to 8 hours of receiving triiodothyronine orally, and within 24 hours the concentration of tyrosine in plasma has been shown to increase from normal values of 11.8 ± 0.4 to 18.0 ± 0.8 μg. per ml. [*3*]. These values are almost identical with those found in spontaneously occurring Graves' disease [*4*].

Conversely, the levels of tyrosine in plasma of hypothyroid subjects are diminished, although to a lesser degree. The mean levels in plasma obtained before breakfast average 9.8 ± 0.6 μg. per ml. in hypothyroid subjects. After the ingestion of tyrosine, plasma levels remain below those of similarly treated euthyroid subjects for as long as 6 hours [*4*].

The elevation of tyrosine levels in hyperthyroidism is especially noteworthy because the total concentration of alpha amino nitrogen in plasma in these patients is normal [*1,3*]. Of the numerous amino acids which have been measured in plasma of hyperthyroid patients, the concentrations of only tyrosine and glutamic acid are increased. Further evidence for the specificity of the changes in tyrosine metabolism is that tryptophan and phenylalanine levels in normal subjects are unchanged following treatment with large doses of triiodothyronine [*3*].

Studies to investigate the pathogenesis of hypertyrosinemia in hyperthyroidism have been conducted both in animals and in man. The major site of tyrosine degradation is in the liver, in which a series of reactions occur leading eventually to the formation of carbon dioxide and water. (Fig. 1.) It is known largely from experiments in rats that the hepatic activity of the first enzyme in this major degradative sequence, tyrosine-α-ketoglutarate transaminase, is increased in hyperthyroidism and reduced in hypothyroidism [*5–7*]. Since the activity of tyrosine-α-ketoglutarate transaminase changes in the same direction as the plasma level of tyrosine with altered thyroid function, changes in the activity of this degradative enzyme could not account for the abnormally high plasma levels of tyrosine in thyroid disease. The activity of the second enzyme in this series, which oxi-

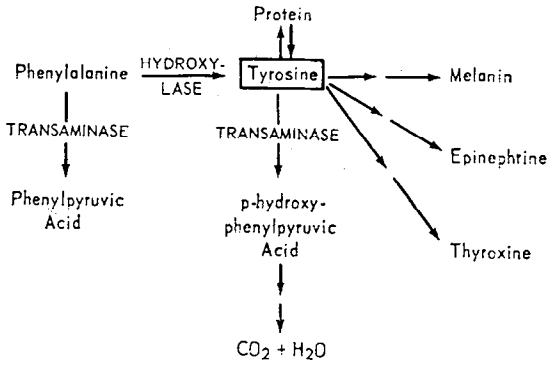

FIG. 1. Diagrammatic representation of the major pathways of tyrosine metabolism. Enzymes are shown in capital letters. Double arrows are intended to signify an entire reaction sequence, the details of which have been omitted.

dizes *p*-hydroxyphenylpyruvic acid, has been reported to decrease [*6*], or to remain essentially unchanged [*8*] by treatment with thyroxine. Conversion of phenylalanine to tyrosine, which is mediated by phenylalanine hydroxylase, is not substantially increased in hyperthyroidism, although a slight decrease occurs in the liver of hypothyroid animals [*9a,b*].

In addition to altering the activities of certain hepatic enzymes, thyroid hormone also produces accelerated turnover of tyrosine [*9a,b*] and a reduction in its apparent volume of distribution [*9a,b*]. In animals treated with thyroid hormone, the free tyrosine content of the thyroid gland is reduced [*9c*]; isolated, perfused livers obtained from these animals show decreased ability to extract tyrosine from the perfusing medium and to retain it intracellularly [*9d*]. The urinary excretion of tyrosine has been reported to increase in clinical hyperthyroidism [*10*]. Although the pathogenesis of hypertyrosinemia has thus not been elucidated, it is likely that several of these factors are of importance.

It is apparent that altered thyroid function produces certain changes in the metabolism of tyrosine, but it is less clear whether a change in tyrosine metabolism alters thyroid function. The oxygen consumption has been variously reported to decrease [*11*] or to undergo no change [*12*] following administration of tyrosine. On the other hand, the addition of tyrosine to a protein-deficient diet increases the uptake of radioactive iodine by the thyroid gland of rats [*13*]. The thyroid-stimulating hormone has been reported to accelerate the uptake of tyrosine by the chick thyroid gland, but uptake of other substances such as arginine is also stimulated under these conditions [*14*]. The studies reported to date do not permit one to arrive at any definite conclusions about possible effects of tyrosine upon the metabolism of the thyroid gland.

A clearly demonstrable effect of tyrosine in animals, and one which has not been widely appreciated, is that dietary administration of this amino acid produces characteristic, reproducible toxicity. The addition of tyrosine in amounts of 1 to 3 per cent to the diet of young white rats produces marked loss of weight, serious ocular changes including keratitis and conjunctivitis, alopecia, hyperkeratosis, inflammation of the extremities, and pancreatic necrosis with diabetes. If continued, death ensues [*12,15,16*]. The severity of the manifestations and the rapidity with which they develop appear to be related to the quantities of tyrosine ingested. It is important to note that administration of thyroid hormone markedly accelerates the development of these pathologic changes, whereas thiouracil has a protective effect. Thyroid hormone given alone, without concurrent ingestion of excessive amounts of tyrosine, will not produce the syndrome of tyrosine toxicity [*12*]. In patients with thyrotoxicosis and in euthyroid human subjects, the administration of tyrosine orally in a single dose has been shown to be devoid of untoward effects [*4,17*]; the results of long-term administration of high tyrosine diets have not, however, been evaluated in man.

It is interesting to compare the plasma profile of amino acids in hyperthyroidism with that observed in the disease of protein malnutrition, kwashiorkor. In the latter, the levels of tyrosine and of other amino acids are depressed [*18–20*]. Relative to phenylalanine, the level of tyrosine is particularly low, and it has been postulated that the conversion of phenylalanine to tyrosine is reduced [*20*]. Treatment of such patients with a high protein diet restores the levels of tyrosine to normal.

One might expect some degree of hypothyroidism to develop in phenylketonuria, since there is a block in the conversion of phenylalanine to tyrosine. The plasma levels of tyrosine may be somewhat reduced in these patients [*21*]. Thyroid function, however, appears to be entirely normal in patients with phenylketonuria [*22,23*]. It is likely that other sources of tyrosine are generally adequate to maintain normal intrathyroidal hormone synthesis, even with a reduction in the rate of formation of tyrosine from phenylalanine.

It is curious that the levels of tyrosine in the plasma of patients with hyperthyroidism closely resemble those found in patients with liver disease. For many years it has been recognized that liver disease can result in high fasting levels and increased urinary excretion of tyrosine, as well as impaired response to an administered load of tyrosine [24–26]. This occurs in either hepatitis or cirrhosis [4].

Recently, several patients have been described with so-called tyrosinosis or tyrosinemia who have had severe cirrhosis in association with elevated plasma levels of tyrosine, and increased excretion of tyrosine metabolites in the urine [27–30]. Renal defects have also been described and may contribute to the altered profile of amino acids. Certain cases of the syndrome may be due to an inborn error of metabolism. The suggestion has been made that there is a block involving the oxidation of *p*-hydroxyphenylpyruvic acid [29]. It is not known whether cirrhosis alone accounts for the elevated plasma levels of tyrosine, or whether they develop independently. The pertinence of tyrosinemia to studies of hyperthyroidism lies in the circumstance that liver alterations of varying severity may occur in patients with hyperthyroidism [31–34], and may make some contribution to the disturbances in tyrosine metabolism described.

Studies of the plasma levels of tyrosine in patients with altered thyroid function suggest certain practical applications. The response to an oral load of tyrosine in patients with hyperthyroidism has been sufficiently consistent to permit its possible application as a test of thyroid function. This test is based upon principles different from those in the routine evaluation of thyroid function. The response to ingestion of tyrosine does not appear to be modified by previous administration of radioisotopes for other diagnostic purposes or by exogenous iodine, and is normal in pregnant women [4]. Nor does the abnormal tolerance to tyrosine which hyperthyroid subjects exhibit seem to be influenced by age or sex. Although fuller experience is certainly required, tests of tyrosine tolerance may have some utility, particularly in conditions such as pregnancy in which it is difficult to apply the usual tests of thyroid function [35].

Measurements of the plasma levels of tyrosine in hyperthyroidism have also been employed to investigate enzyme induction. It is well known that corticosteroids produce large and rapid increases in the activity of a number of important hepatic enzymes [36]. Effects of hormones upon enzymes may constitute one of the major mechanisms for regulation of metabolism. This process has been extensively studied in experimental animals, but has received comparatively little attention in man. The finding that cortisone in amounts commonly used therapeutically depresses the concentration of tyrosine in plasma of euthyroid and hypothyroid subjects is strong evidence of the functioning of a cortisone-inducible tyrosine transaminase in human liver [37]. That similar doses of cortisone will not depress the plasma level of tyrosine in hyperthyroid subjects is evidence that the process of enzyme induction is significantly modified in a manner similar to that described in experimental animals [38]. The clinical importance of enzyme induction in man as a determinant of responsiveness to drugs has been discussed by Burns [39]. Enzyme induction may explain the stimulatory effects of some drugs upon their own metabolism, and the refractoriness to certain other drugs which may develop after their long-term administration.

At present, the over-all significance of elevated plasma levels of tyrosine in hyperthyroidism is completely unknown. Several questions are raised: Is tyrosine present in excessive amounts in the diet toxic for man, as it has been shown to be for laboratory animals? Are the abnormal plasma levels of tyrosine responsible for any of the clinical manifestations of thyroid disease? Does the level of tyrosine in plasma influence the formation or release of either thyroid hormones or thyroid stimulating hormones? Or is the elevated level of tyrosine merely a laboratory finding of no particular physiologic importance? Future research should help to provide the answers to these questions.

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