THE SERUM TYROSINE LEVEL AS AN INDEX OF THYROID FUNCTION

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SUMMARY

Serum tyrosine was measured in 22 normal subjects, 17 patients with non-toxic goitre, ten patients with hypothyroidism, 37 patients with thyrotoxicosis and eight geriatric patients. Low values were obtained in hypothyroidism and high values in thyrotoxicosis. In thyrotoxicosis there was only a small overlap with the euthyroid subjects. Thus, measurements of serum tyrosine appear to be a useful test for the diagnosis of hyperthyroidism, not invalidated by previous iodine administration and not involving the use of radio-isotopes. Administration of vitamin C reduced the increased values of tyrosine in thyrotoxicosis to normal levels. It is suggested that a latent vitamin C deficiency may partly explain the increase in the serum tyrosine values in thyrotoxicosis.

INTRODUCTION

Serum or plasma tyrosine concentration is increased in patients with thyrotoxicosis and decreased in subjects suffering from hypothyroidism (Levine, Oates, Vendsalu & Sjoerdasma, 1962; Melmon, Rivlin, Oates & Sjoerdasma, 1964). The mechanism underlying these changes is not entirely clear, but Melmon et al. (1964) have suggested that the plasma tyrosine level, in the fasting state or after an oral loading dose of tyrosine, may be used as an index of thyroid function. Confirmation of these findings would be of practical importance, since the plasma tyrosine level can be readily measured without the use of isotopes. Furthermore, the plasma tyrosine level would fall into the category of tests reflecting the altered response of the peripheral tissues to abnormal amounts of thyroid hormones, such as the basal metabolic rate, the serum cholesterol level and the Achilles tendon reflex (Wayne, Koutras & Alexander, 1964). Since none of these is entirely satisfactory, the assessment of other tests is indicated. However, in order to be suitable for clinical practice, a test must show not only a significant difference between the mean values of the normal and abnormal groups studied, but also no substantial overlap of the abnormal and normal ranges. In order to study the extent of this overlap, a larger number of patients was examined than in previous reports. Furthermore, the plasma tyrosine level was related to serum protein-bound iodine (PBI). The effect of milk intake, vitamin C and iodine administration on the results of the test was also studied.
MATERIALS AND METHODS

Serum tyrosine was measured by the method of Udenfriend & Cooper (1952). This method involves reaction with nitrosonaphthol, in nitric acid, to yield unstable red-coloured derivatives. If the reaction continues for a longer time and at a high temperature, the red intermediate changes to a stable yellow compound. Excess nitrosonaphthol, which is yellow itself, can then be extracted from the reaction mixture with ethylene dichloride. This method does not distinguish between tyrosine and tyramine, but, normally, serum contains no significant amounts of tyramine.

Blood samples were obtained in the morning after an overnight fast from patients who had not taken food containing protein during the preceding day. Although no significant change in the tyrosine content of serum was observed after storage at 4° for 1 month, the assays were routinely performed not later than 10 days after collection of the samples.

The normal range of serum tyrosine concentrations was established in hospital controls without any evidence of thyroid disease or other metabolic disorders. The patients with thyroid disease investigated were diagnosed at the Thyroid Clinic of the ‘Alexandra’ Hospital by clinical examination and radio-isotopic studies (Malamos, Daikos, Samara & Koutras, 1959) and confirmed, in most cases, by a serum PBI estimation by the manual method of Benotti & Benotti (1963). In addition, serum tyrosine was estimated in eight debilitated geriatric patients (all female, aged 70 yr. or more). In three normal persons serum tyrosine was estimated on three consecutive days in order to define the extent of spontaneous variations.

In eight thyrotoxic patients serum tyrosine was estimated before and after oral vitamin C administration (600–1500 mg./day) for at least 3 days. In five euthyroid patients serum tyrosine was estimated before and after a 7-day course of L-triiodothyronine (120 µg./day) orally. In three normal subjects serum tyrosine was measured in the fasting state and at intervals after drinking 500 ml. of milk.

Table 1. Serum tyrosine concentration (µmole/100 ml.) in various conditions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of subjects</th>
<th>Mean</th>
<th>S.D.</th>
<th>S.E.</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>22</td>
<td>6·8</td>
<td>0·6</td>
<td>0·14</td>
<td>4·8–8·2</td>
</tr>
<tr>
<td>Non-toxic goitre</td>
<td>17</td>
<td>6·4</td>
<td>1·2</td>
<td>0·30</td>
<td>3·7–8·5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>10</td>
<td>5·0</td>
<td>1·1</td>
<td>0·35</td>
<td>3·7–6·7</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>37</td>
<td>12·2</td>
<td>3·1</td>
<td>0·52</td>
<td>8·4–20·6</td>
</tr>
<tr>
<td>Geriatric</td>
<td>8</td>
<td>6·5</td>
<td>1·4</td>
<td>0·48</td>
<td>4·4–8·5</td>
</tr>
<tr>
<td>After iodine</td>
<td>5</td>
<td>7·3</td>
<td>—</td>
<td>—</td>
<td>6·7–8·1</td>
</tr>
</tbody>
</table>

RESULTS

The results are shown in Table 1 and Figs. 1–3. Normal subjects had a fasting serum tyrosine level (mean ± s.e.) of 6·8 ± 0·14 µmole/100 ml., which was significantly different from the value of 5·0 ± 0·35 obtained in hypothyroid patients (P < 0·001) and 12·2 ± 0·52 in thyrotoxicosis (P < 0·001). Cases of non-toxic goitre had a mean value of 6·4 ± 0·30 µmole/100 ml., not significantly different from normal. In eight geriatric patients the serum tyrosine did not show any significant difference from the normal range. In three normal persons the serum tyrosine concentration was measured on
Tyrosine level and thyroid function

Fig. 1. Serum tyrosine concentrations in various conditions. The broken lines enclose the normal range of 4.5–8.3 μmoles/100 ml.

Fig. 2. The correlation of serum tyrosine levels with values for protein-bound iodine (PBI). The correlation coefficient is $r = +0.766$, and the regression equation $y = 4.4 + 0.55x$. 

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three consecutive days. The difference between any two estimations from the same subject ranged from 0·0 to 0·3 µmole/100 ml.

Fig. 1 and Table 1 show that the observed normal range was 4·8–8·2 µmole/100 ml.; the statistical normal range (mean ± 2 s.d.) was 5·5–8·1. If the other euthyroid groups (non-toxic goitre and geriatric) are included the normal range becomes 3·7–8·5 µmole. In Fig. 1 the values 4·5 and 8·3 µmoles have been chosen as the limits of the normal range which give the best separation between the euthyroid cases and those with altered thyroid function. There was no overlap between the normal subjects and the thyrotoxic patients, whereas hypothyroid values overlapped extensively with the normal range (5 out of 10). Cases of non-toxic goitre or geriatric patients fell generally within the normal range.

A fair correlation between serum PBI and serum tyrosine is shown in Fig. 2. The correlation coefficient (r) is +0·766, significantly different from zero (P < 0·001), but the regression equation tyrosine = 4·4 ± 0·55 PBI shows an intercept well up on the ordinate. It can also be calculated from the correlation coefficient that 58% of the variation in the serum tyrosine is dependent on the variation of the PBI.

Figure 3 shows that drinking 500 ml. milk by normal subjects results in a prompt rise in the serum tyrosine level. In one case, followed for 5 hr., the serum tyrosine returned to the fasting value, but in the two other cases, followed for less than 4 hr., the serum tyrosine level remained high.

After administration of large quantities of organic iodine-containing compounds as radio-opaque contrast media during pyelography or cholecystography to five patients, the serum tyrosine level did not show any striking difference from normal (Table 1), all the values being within the normal range.

Administration of vitamin C to eight thyrotoxic patients resulted in a decrease of the serum tyrosine level to normal values. The mean difference of –2·3 ± 0·57 µmole/100 ml. was significantly different from zero (P < 0·005).
In five euthyroid subjects who received triiodothyronine, there was a slight increase of the serum tyrosine level over the pretreatment value (mean difference $-0.8 \pm 0.89 \mu$ mole/100 ml), not significantly different from zero.

DISCUSSION

The present results confirm that serum tyrosine is increased in hyperthyroidism and decreased in hypothyroidism, but the mechanism underlying these alterations requires elucidation. The most probable explanation is a decreased rate of tyrosine degradation in thyrotoxicosis. The metabolism of tyrosine has been recently elucidated and comprises several steps. First, tyrosine is transaminated to $p$-hydroxyphenylpyruvate, which is successively oxidized to homogentisic acid, maleic-acetic acid, fumaric-acetic acid and, finally, to fumaric and acetoacetic acid. Thyroxine administration to rats increases tyrosine transaminase activity in the liver (Rivlin, 1963; Rivlin & Levine, 1963). Therefore, the action of thyroid hormones in the first step of tyrosine metabolism should result in a decrease, rather than an increase, of the serum tyrosine level. However, the second and third steps of tyrosine degradation depend on vitamin C (Suda, Takeda, Sujishi & Tanaka, 1951; Zannoni & LaDu, 1960). Thus, our finding that the administration of vitamin C to thyrotoxic patients decreased serum tyrosine to normal levels may be relevant to the occurrence of latent vitamin C deficiency in thyrotoxicosis (Lewis, 1938; Drill, 1943; and unpublished findings).

Whatever the mechanism of the changes in tyrosine concentration, estimations of tyrosine may provide a convenient way to assess thyroid function in clinical practice. The results presented above show only a slight overlap between euthyroid groups (normal controls, geriatric cases and patients with non-toxic goitre) and the hyperthyroid cases. On the other hand, half the hypothyroid patients overlapped with the normal range. While this manuscript was in preparation, Rivlin, Melmon & Sjoerdsma (1965) published a paper suggesting an oral tyrosine tolerance test for the diagnosis of thyrotoxicosis and myxoedema. Our findings show that it is not usually necessary to administer tyrosine, at least for the diagnosis of thyrotoxicosis, since good separation between normal subjects and thyrotoxic patients can be achieved by determination of the level of endogenous tyrosine during the fasting state.

The diagnostic accuracy of the fasting serum tyrosine concentration in thyrotoxicosis compares favourably with other tests of thyroid function. Figure 1 shows that the overlap is not greater than that previously reported by Alexander, Koutras, Crooks, Buchanan, MacDonald, Richmond & Wayne (1962) for estimations of PBI, the $^{131}$I uptake in 2½ hr. and the values for absolute iodine uptake (AIU) by the thyroid. The separation from normal subjects is probably better than that achieved by estimations of the basal metabolic rate, serum cholesterol or the Achilles tendon reflex in thyrotoxicosis.

All these tests of thyroid function which are based on the peripheral effect of thyroid hormones can never be entirely specific, since metabolic processes usually depend on an interplay of several factors. Tyrosinosis as an inborn error of metabolism is so rare as not to interfere significantly with the diagnostic accuracy of serum tyrosine estimations. As shown in this paper, vitamin C administration may, under
certain conditions, induce a decrease of the elevated values found in untreated thyrotoxicosis and it seems theoretically justifiable to expect increased levels in scurvy. Non-specific debility due to old age does not influence the serum tyrosine level, but Matthews & Partington (1964) have found increased values in premature babies ingesting more than 5·0 g. of protein/kg./day. Probably, several other conditions or drugs influence serum tyrosine, but these remain to be defined. Nevertheless, since our euthyroid groups, consisting of patients in hospital with a variety of medical disorders, showed only a small overlap with the thyrotoxic patients, measurements of fasting serum tyrosine levels appear to have an acceptable degree of specificity.

An advantage of serum tyrosine estimations is that they are more reliable in thyrotoxicosis, in which the other tests depending on peripheral effects of the thyroid hormones, such as measurements of the basal metabolic rate, of the serum cholesterol level and the Achilles tendon reflex, give less reliable results than in hypothyroidism. Measurements of serum tyrosine are not affected by previous administration of iodine in pharmacological doses, and may thus prove especially valuable in this situation, in which both the use of radioactive iodine and PBI determinations are invalidated. Finally, no radioactive substance is administered to the patient.

REFERENCES


