Biogenic amines and thyrotoxicosis

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Circulating levels of T3, T4, γ-amino-butyric acid, glutamate, 5-hydroxytryptamine, histamine, monoamine oxidase and histaminase were studied in 45 (25M, 20F) hyperthyroid patients and 46 (25M, 21F) normal healthy volunteers. Increased levels of blood 5-hydroxytryptamine, histamine and glutamic acid were observed along with elevated T3 and T4, whereas plasma γ-aminobutyric acid, monoamine oxidase and histaminase activities were found to be low in both male and female patients. After three months of treatment, circulating levels of 5-hydroxytryptamine, histamine and glutamic acid decreased significantly along with normalization of thyroid hormones and with an increase in the concentrations of γ-aminobutyric acid, monoamine oxidase and histaminase. There was a positive correlation between these amines and thyroid hormone levels. The findings thus suggest that alterations in the metabolism of biogenic amines may be related to an altered metabolism in thyrotoxicosis, and these parameters may prove to be useful markers for diagnosis and follow-up of these patients.

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Biogenic amines play an important role in the regulation of many physiological and psychological processes. Recently, considerable attention has been paid to evaluating the effect of biogenic amines on thyroid function. It has been observed that not only TSH but also long-acting thyroid stimulator (LATS) may interact with biogenic amines (1). Experimental studies have also shown a close association between biogenic amines and thyroid function. It has been reported that 5-hydroxytryptamine (5-HT) activity stimulates iodine metabolism in isolated thyroid cells which leads to the formation of iodothyronines, this effect being similar to that of catecholamines (2). Ericson et al. (3) showed that both 5-HT and catecholamines stimulate thyroid hormone release in vivo. Further, 5-hydroxytryptophane is known to elevate TSH secretion in rats and humans (4, 5), and it has been reported that intravenous injection of histamine H2 agonist enhances T3 response to TRH and thus interacts with thyroid function. Sanchez Herrenz et al. (6) on the other hand reported that γ-aminobutyric acid (GABA) inhibits TSH release in experimental animals. Thus, it was considered to be of interest to study the metabolic status of these amines in hyperthyroid patients in order to elucidate the possible association of these amines with thyroid dysfunction.

Patients and methods

We studied 46 (25M, 21F) normal healthy volunteers (as controls), aged 25 to 45 years, non-obese, with normal endocrine and metabolic functions, and with no family history of thyrotoxicosis; and 45 (25M, 20F) hyperthyroid patients, aged 20 to 50 years. The diagnosis of thyrotoxicosis was based on clinical profile and biochemical investigations including measurements of serum T3 and T4 (RIA methods). All the subjects were selected from the Thyroid Clinic of S.S. Hospital, Institute of Medical Sciences, Banaras Hindu University. None of the controls were taking any drug or intoxicants like alcohol, marijuana, tobacco, etc., and all were consuming a normal diet. Blood samples were collected from each subject in the fasting state between 09.00 and 10.00 in the supine position. A total of 4 ml blood was taken separately in each tube containing double oxalate and heparine as anti-coagulants for the measurement of biogenic amines, and 2 ml in a plain vial for the estimation of serum T3 and T4. Elution was done from double oxalated blood, whereas plasma and serum were separated from heparinized and plain vial samples, respectively. All the samples were placed at −20°C and used for the estimation of biogenic amines and thyroid hormones. Follow-up studies were carried out at three-month intervals and the blood samples were again collected in the same way. Patients with thyrotoxicosis were treated with carbimazole tablets, 45–60 mg per day (divided dose). The pretreatment body weight of patients ranged from 40 to 70 kg and the duration of thyrotoxicosis was from two to six months.

Plasma 5-HT level was assayed using the method of Snyder et al. (7); blood histamine was estimated using
the technique of Shore et al. (8). Plasma histaminase and MAO activity were assayed using the method of Arsen and Kemp (9) and Pervez and Pervez (10), respectively. GABA and glutamate were determined using the method of Saito and Tokunaga (11).

Serum T₃ and T₄ were measured by RIA technique using the kits obtained from Bhabha Atomic Research Centre, Trombay, Bombay, India. Statistical analysis was carried out using the Student’s t-test and paired t-test. Further, the correlation coefficients between biogenic amines and T₃ and T₄ were calculated by using Pearson’s formula.

Results
Considerable elevation of circulating levels of 5-HT and histamine and decreased levels of monoamine oxidase (MAO) and histaminase were recorded in hyperthyroid patients. Plasma glutamic acid level was also higher in both male and female patients along with thyroid hormones (T₃ and T₄). The GABA level was found to be low compared with controls (Table 1). No significant difference was observed between male and female patients, though in females the level of histamine, MAO, histaminase, T₃ and T₄, and glutamic acid were slightly higher than in males (Table 1). A marked reduction in 5-HT and histamine levels was noticed in both clinical groups following three months of treatment. MAO and histaminase activity increased in the treated groups. There was a significant elevation of GABA compared with controls. Circulating levels of T₃ and T₄ decreased significantly following treatment in both male and female patients. Plasma glutamic acid level also decreased significantly both in male and female patients (Table 1).

Linear regression analysis of biogenic amines vs thyroid hormones
The data obtained from male and female hyperthyroid patients were combined and subjected to linear regression analysis. Highly significant correlation was obtained between serum T₃ and 5-HT (N = 45, r = 0.522, p < 0.01), T₃ and GABA (N = 45, r = 0.822, p < 0.001), T₄ and MAO (N = 45, r = 0.577, p < 0.01) and T₄ and histamine (N = 45, r = 0.741, p < 0.001). This is shown in Figs. 1, 2, 3 and 4, respectively. But there was lack of correlation between T₃ and T₄ and other parameters studied.

Discussion
In the present study hyperthyroidism was found to be associated with increased circulating levels of 5-HT, histamine and glutamate, and with a decreased activity of MAO, histaminase and GABA. It is well known that synthesis and degradation of 5-HT is catalysed by the enzymes aromatic amino acid decarboxylase and MAO, respectively. Thus, quite possibly the increased level of plasma 5-HT could be due to either increased synthesis or decreased degradation or both. As 5-HT may stimulate thyroid hormone secretion as well as thyroid blood

Table 1. Circulating levels of T₃, T₄, MAO, 5-HT, histamine, histaminase, GABA and glutamate in hyperthyroid patients and normal controls. Values are mean ± SEM. For all comparisons, A vs B, B vs C, D vs E and E vs F, p-values (two-tailed) were below 0.00001 (except for glutamate, E vs F: p < 0.0001).

<table>
<thead>
<tr>
<th></th>
<th>Normal ranges</th>
<th>Normal controls</th>
<th>Patient groups</th>
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<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>No.</td>
<td>25</td>
<td>21</td>
<td>25</td>
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<tr>
<td>T₃ (nmol/l)</td>
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<td>0.77</td>
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<tr>
<td>T₄ (nmol/l)</td>
<td>-4.15</td>
<td>-4.92</td>
<td>±0.22</td>
</tr>
<tr>
<td>MAO (nmol·l⁻¹·h⁻¹)</td>
<td>-154</td>
<td>-167</td>
<td>±5</td>
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<tr>
<td>5-HT (µmol/l)</td>
<td>1940</td>
<td>2340</td>
<td>3350</td>
</tr>
<tr>
<td>Histamine (µmol/l)</td>
<td>±4530</td>
<td>±5630</td>
<td>±160</td>
</tr>
<tr>
<td>Histaminase (AU/l)</td>
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<td>0.24</td>
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<td>GABA (µmol/l)</td>
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<td>±0.05</td>
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<td>5-HT (µmol/l)</td>
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<td>31000</td>
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<td>(ng/l)</td>
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Fig. 1. Linear regression analysis of serum $T_3$ vs plasma 5-HT in hyperthyroid patients. $Y = 0.1122 X + 1.2512$, $r = 0.522$.

Fig. 2. Linear regression analysis of serum $T_3$ vs plasma GABA in hyperthyroid patients. $Y = 30.0156 X + 172.3650$, $r = 0.822$.

Fig. 3. Linear regression analysis of serum $T_3$ vs plasma MAO activity in hyperthyroid patients. $Y = 131.4548 X + 416.0897$, $r = 0.577$.

Fig. 4. Linear regression analysis of serum $T_4$ vs blood histamine in hyperthyroid patients. $Y = 0.0100 X - 0.5747$, $r = 0.741$. 
flow (1, 3, 12), it is possible that the increased level of plasma 5-HT in hyperthyroidism augments the hypersecretion of thyroid hormone.

The increased circulating level of histamine in hyperthyroid patients may possibly be due to decreased activity of histaminase, a degrading enzyme for histamine. Further, the decreased plasma MAO activity observed in these patients may possibly also be a contributory factor for an increase in histamine level, as non-selective MAO inhibitors have been reported to elevate circulating levels of histamine. It seems possible that histamine directly interacts with thyroid axis because histidine (a precursor of histamine) deficiency leads to a reduction of histidine in serum along with decreased concentration of thyroxine (13).

Similarly, ranitidine (a histamine antagonist) administration is known to decrease basal concentration of T₄ in man (14), thus suggesting a direct action of histamine on thyroid axis. Similarly, the increased histamine level in these patients may elevate T₃ concentration, because administration of cimetidine, a histamine antagonist, results in a decreased level of T₃ (15). It may also be possible that circulating levels of histamine influence intrathyroidal concentration of histamine, which is known to participate in thyroid hormone release.

Thus, it seems possible that elevated concentrations of 5-HT and histamine in these patients may be associated with enhanced thyroid activity. After three months of treatment, a marked reduction in thyroid hormones was observed along with decreased levels of amines. Carbimazole treatment possibly alters T₃ and T₄ levels through its effect on 5-HT and histamine levels as, with treatment, a marked reduction of thyroid hormones has been observed with a decrease in 5-HT and histamine levels.

Circulating levels of GABA were decreased in hyperthyroid patients, while glutamate level was increased. It appears that in hyperthyroid state a rapid conversion of glucose into glutamate takes place which enriches the metabolic pool of glutamate, resulting in its level being increased under such situations. An increased level of γ-aminobutyric acid transaminase may also be one of the causes for the decreased GABA concentration in these patients. Further, GABA showed increasing trend after carbimazole treatment, which shows that the drug potentiates the effect of GABA by increasing the glutamic acid decarboxylase activity or by reducing the GABA-transaminase activity. The lower value of glutamate produced by carbimazole may be used in its metabolic pathway for the synthesis of GABA which was found to increase after treatment.

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References
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