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Biogenic amines metabolism and blood chemistry of psychiatric patients

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Summary
The metabolism of biogenic amines and blood chemistry of psychiatric patients were investigated. Eighty newly admitted psychiatric patients suffering from schizophrenia, hypomania, mania and paranoid disorder, and matched with fifteen normal subjects were used for the study. Blood was collected and centrifuged, after which serum was extracted. Serum concentrations of biogenic amines, namely epinephrine, norepinephrine, dopamine and serotonin were determined using spectrofluorimetric method. Serum concentration of 5-HIAA, activities of alanine transaminase and aspartate transaminase were determined. The concentrations of serum protein, albumin, Na^+, K^+, Cl^- and CO_2 in the psychiatric patients and control subjects were determined using Synchron CX5 automated spectrophotometer. Results of the study showed that the concentrations of serum epinephrine and norepinephrine in the psychiatric patients were significantly increased, while the concentrations of dopamine and serotonin were significantly decreased, as compared with the controls. Serum 5-HIAA levels were significantly elevated in all psychiatric patients compared with the controls. There was a marked elevation of the activities of alanine transaminase and aspartate transaminase in all psychiatric syndromes, with the exception of paranoid disorder, which was reduced. Data of the study indicate that metabolism of biogenic amines and concentrations of serum proteins, enzymes and some electrolytes were significantly affected in psychiatric patients suffering form schizophrenia, hypomania, mania and paranoid disorder.

Keywords: *Biogenic amines, blood chemistry, psychiatric syndromes.*

Résumé
Le métabolisme des amines biogéniques et la réaction sanguine des malades mentaux ont été étudiés. Quatre vingt nouveaux malades mentaux hospitalisés et souffrant de la schizophrénie, l' hypomanie, la manie et des desordres paranoïdes, et quinze autres personnes saines ont été utilisé pour cette étude. Le sang a été prélévé et centrifugé aprés quoi le sérum a été extrait. Les concentrations de sérum des amines biogéniques à savoir l'adrénaline,nonadrénaline, la dopamine et le serotonin ont été déterminés en employant la méthode spectrofluorimétrique. La concentration de sérum 5–HIAA, les activités transaminase alanine et transaminase aspartate ont été déterminées. Les concentrations de protéine de sérum, l'abumine, Na^+, K^+, Cl^- et CO2 dans les malades mentaux et les personnes de contrôle ont été déterminées en utilisant le spectrophotomètre automatique de marque Synchron CX5. Les résultats de l'étude montrent que les concentrations de sérum d'adrénaline et de noradrénaline dans les malades mentaux sont augumentés considérablement tandis que les concentrations de dopamine et sérotonin sont diminués considérablement et comparativement à celles du groupe de contrôle. Les niveaux de sérum 5–HIAA étaient considérablement élévés dans tous les malades mentaux en comparaison avec celui du groupe de contrôle. Il y avait une élévation remarquable des activités de transaminase alamine et de transaminase aspartate dans tous les syndromes psychiatriques à l'exception des desordres paranoïdes qui étaient reduits. Les données de l'étude indiquent que le métabolisme des amines biogénique et les concentrations de protéines de sérum, les enzymes et quelques électrolites ont été considérablement affectés dans les malades mentaux souffrant de schizophrénie, hypomanie, manie et des désordres paranoïdes.

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Introduction

Affective disorders are characterized by inappropriate depression or elation. Abnormalities in perception and cognition may also occur but arise out of the mood disturbance [1]. A growing body of evidence indicates that biochemical factors play an important role in the aetiology of at least some forms of mental disorders. The biogenic amines of interest in relation to psychiatric syndromes, such as schizophrenia, hypomania, mania and paranoid disorder are epinephrine, norepinephrine, dopamine and serotonin [2]. These biogenic amines serve as neurotransmitters, the catecholamines (epinephrine, norepinephrine and dopamine) and serotonin are synthesized from tyrosine and tryptophan [3].

Re-uptake is the principal mechanism by which catecholamines, and other monoamines are inactivated after having transmitted information from one neuron to the other [3]. It has been that compounds such as methyldopa, can suppress catecholamine activity in the brain, and can also provoke depression in humans [4]. Therefore, there may be a possible relationship between central catecholamine deficiency and the development of certain depressive symptoms.

It is therefore very important to study the levels of biogenic amines, the metabolites and metabolizable enzymes in psychiatric patients, to ascertain if neurotransmitter levels, serum protein, albumin and electrolytes were affected.

The electrolyte balance in human blood interestingly, plays a vital role in the release of electrical impulses, that facilitate neurotransmitter release, for instance, calcium remains a key factor in the re-uptake of deactivated neurotransmitter for reactivation and subsequent usage [5].

There have been biochemical hypothesis in the aetiology and pathogenesis of some psychiatric syndromes, but the majority of investigations have attempted to demonstrate an association between these disorders and aberrant brain function of monoamine mechanisms, amino acid neurotransmitters and neuropeptides [5,6]. For example, the monoamine hypothesis postulates that depression is due to a deficiency of monoamine neurotransmitters of certain strategic sites in the brain, and mania results from an excess [5,6].

In the present study, we have selected some of the common psychiatric syndromes, such as schizophrenia, hypomania, mania and paranoid disorder for investigation. Schizophrenia is a prevalent mental disorder that is emotionally crippling and costly both financially and to interpersonal relationship [6]. Hypomania is characterized by increased speech and physical activity, while mania is characterized by elation, pressure of speech and physical hyperactivity [7]; paranoid disorder is characterized by self reference, immense sensitivity to others and an unreasonable degree of suspiciousness about their actions and motives [8].

From the wealth of literature, there is scanty report on the metabolism of biogenic amines, and blood chemistry of psychiatric patients. Direct investigations of brain serotoninergic mechanisms in schizophrenia have also been carried out on postmortem tissues. Joseph *et al* [10] measured the brain concentrations of tryptophan, 5-hydroxy tryptamine (5-HT) and 5-hydroxy indole acetic acid (5-HIAA), and found no evidence of changes in 5-HT metabolism associated with schizophrenia. In addition, Toru *et al* [11] reported that brain 5-HIAA were similar in controls and schizophrenia. Clearly, there is a need for additional investigations of the metabolism of biogenic amines in affective disorders.

Therefore, the present study is designed to ascertain if or to what extent biogenic amine levels, specifically epinephrine, norepinephrine, dopamine and serotonin; serum proteins, albumin and some electrolytes are affected in these psychiatric syndromes, namely schizophrenia, hypomania, mania and paranoid disorder.

Subjects and methods

Eighty newly admitted psychiatric patients were studied. They were rated according to psychiatric status-rating scales [6, 12]. The patients were voluntarily admitted to psychiatric clinics at the Department of Psychiatry, College of Medicine, University of Lagos, Lagos. The subjects were psychiatric patients suffering from schizophrenia, hypomania, mania and paranoid disorder.

Fifteen healthy control subjects were recruited from hospital staff. The nutritional status of the patients and controls were assessed based on the dietary history, body weight and blood investigation for plasma proteins [13]. They all consumed balanced diets, had normal body weight for age and normal plasma protein levels, with no clinical sign of malnutrition. The study protocol was approved by the Ethics and Experimentation Committee of the Lagos University Teaching Hospital (LUTH). Written informed consent was obtained from all participants. 20 ml of blood was collected intravenously from each patient and control subject.

The mean age of the patients was 26 ± 5 years, while that of the controls was 27 ± 4 years. There were 68 male and 12 female patients, while the normal controls were 12 males and 3 females. The subjects were drug-free prior to a minimum of seven days. Blood samples were collected between 0830h and 0930h in a fasting condition and allowed to stand at room temperature for 15 min after which it was centrifuged at 3,000g for10 min in a Beckman Model T-6 refrigerated centrifuge.

Determination of serum biogenic amines

The concentrations of epinephrine, norepinephrine, dopamine and serotonin in the serum were determined according to the methods of Kari *et al.* [14] and Udenfriend *et al.* [15]. These methods consist of extraction of the different brain biogenic amines followed by the spectrofluorimetric detection using the Amino-Bowman spectrofluorimeter. The amine content was calculated by comparison with the internal standard based on the modified method of Ansell and Beeson [16].

Determination of serum 5-hydroxy indole acetic acid concentration

Serum 5-HIAA concentration was determined using the methods of Kari *et al.* [14] and Udenfriend *et al.* [15].

Assay of enzyme activity

The activities of alanine (ALA) transaminase and aspartate (AST) transaminase in the sera of psychiatric patients and normal control subjects were determined using the Synchron CX5 automated spectrophotometer (Beckman, Switzerland).

Measurement of serum proteins, albumin and electrolytes

The chemical analyses of protein, albumin, Na+, Cl- and CO_2 levels in the sera of the psychiatric patients and control subjects were carried out using the Synchron CX5 automated spectrophotometer.

Statistical analysis

The results are expressed as mean ± S.E.M., and "n" denoted the number of human subjects used for each experiment. Data were subjected to analysis of variance [17], while significant differences were further tested by the Duncan's test [18].

Results

The concentrations of serum biogenic amines of psychiatric patients and normal subjects are presented in Table 1. The concentrations of serum epinephrine in patients suffering from all the psychiatric syndromes investigated in this study were significantly ($P < 0.01$) increased, as compared with the controls. There were significant differences in the serum norepinephrine levels of all the psychiatric syndromes, as compared with the controls. The serum norepinephrine levels in all the psychiatric syndromes, were significantly higher than those in the controls. Dopamine and serotonin levels in patients suffering from all the psychiatric syndromes studied were significantly ($P < 0.01$) reduced as compared with the controls (Table 1).

Table 1: Concentration of serum biogenic amines (Mean+SE) of psychiatrics patients and normal subject [1,2]

Psychiatric Syndrome	Biogenic Amines Concentration (ug/l) Epinephrine	Norepinephrine	Dopamine	Serotonin
Schizophrenia n=20	0.12±0.020[a]	0.27±0.410[a]	0.31±0.041[a]	0.51±0.063[a]
Hypomania n=20	0.17±0.400[b]	0.26±0.034[a]	0.28±0.032[a]	0.44±0.052[b]
Mania n=20	0.13±0.024[a]	0.26±0.030[a]	0.32+0.025[a]	0.43±0.044[b]
Pramoid Disorder n=20	0.15±0.031[ab]	0.27±0.020[a]	0.31±0.020[a]	0.41±0.060[b]
Control n=15	0.05±0.001[c]	0.23±0.040[b]	0.75±0.063[c]	0.57±0.048[c]

1. n = number of subjects. Triplicate determinations were carried out

2. Values carrying different superscripts (a,b,c,) vertically are significantly ($P < 0.01$) different

However, there was no significant difference in serum the epinephrine level of the schizophreniacs and maniacs, but the valveswere lower in both the hypomaniacs and victims ofparanoid disorder. There were significant differences in the serum dopamine level of the hypomaniacs as compared with the values obtained in patients suffering from schizophrenia, mania and paranoid disorder.

The serum 5-HIAA concentrations and activities of alanine and aspartate transaminase of psychiatric patients and normal control subjects are presented in Table 2. The serum 5-HIAA concentrations in patients suffering from all the psychiatric syndromes investigated, were significantly ($P < 0.01$) higher than those in controls. However, serum 5-HIAA levels in the schizophrenics were significantly higher those than in patients suffering from hypomania, mania and paranoid disorder. Serum 5-HIAA levels in the hypomaniacs were significantly lower than those in patients suffering from mania or paranoid disorders. There was no significant difference in the serum 5-HIAA level of the patients suffering from mania and paranoid disorder.

The mean activities of alanine transaminase in the psychiatric patients were significantly higher than in controls (Table 2). However, ALA transaminase activity in schizophrenics was significantly higher than in patients suffering from hypomania, mania and paranoid disorder. Alanine transaminase activity of the hypomaniacs was significantly higher than in patients suffering from mania and paranoid disorder. There was no marked difference in the activity of ALA transaminase activity in patients suffering from mania when compared with the data obtained in other psychiatric syndromes. Paranoid disorder patients had the lowest activity of ALA transaminase as compared with other psychiatric syndromes.

With the exception of the paranoid disorder patients, the activities of aspartate transaminase in all the psychiatric patients studied were significantly higher than in the control group (Table 2). There was no significant difference in the activity of AST transaminase activity of patients suffering from paranoid disorders and the normal control subjects (Table 2).

Table 2: Serum concentration of 5-hydroxy indole acetic (5-HIAA) and activities of alanine and aspartate transaminase (Mean ± SE) of psychiatric patients and normal subjects. [1,2]

Psychiatric syndrome	5-HIAA Concentration (ug/i)	Alanine transaminase Activity (I.U/I)	Aspartate transminase Activity (I.U/I)
Schizophrenia n=20	0.72 ± 0.06^a	57.9 ± 4.02^a	43.6 ± 2.97^a
Hypomania n=20	0.53 ± 0.056^b	43.3 ± 2.95^b	38.4 ± 3.65^b
Mania n=20	0.64 ± 0.061^c	25.7 ± 2.51^c	45.2 ± 4.82^a
Paranoid Disorder n=20	0.66 ± 0.072^c	19.4 ± 1.53^d	21.7 ± 2.65^c
Control n=20	0.47 ± 0.084^d	14.8 ± 1.14^c	24.1 ± 1.58^c

1. n = number of subjects. Triplicate determinations were carried out for each assay.

2. Values carrying different superscripts (a,b,c) vertically are significantly (P<0.01) different

The results of the serum protein and electrolytes of psychiatric patients and normal control subjects are shown in Table 3. Serum protein concentrations in patients suffering from mania and paranoid disorders were significantly ($P < 0.01$) lower than those in the controls, while those of the schizophrenics and hypomaniacs were not significantly different from those in the controls. The serum albumin concentration in patients suffering from hypomania, mania and paranoid disorders were significantly lower than those in the controls, while those of the schizophrenics was not significantly different from those in the controls (Table 3).

Table 3: Serum proteins and electrolytes (Mean ± SE) of psychiatric patients and normal subject [1,2]

Psychiatric Syndrome	Protein (ug/l)	Serum Albumin (ug/l)	Na^+ (nMol/l)	K^+ (Mmol/l)	Cl^- (mMol/l)	CO_2 (mMol/l)
Schizophrenia n = 20	68.9 ± 7.50^a	40.5 ± 5.80^a	1354 ± 9.64^a	4.45 ± 0.64^a	108.4 ± 7.50^a	21.4 ± 1.07^a
Hypomania n = 20	71.4 ± 6.80^a	33.8 ± 4.21^b	133.1 ± 7.12^a	4.23 ± 0.15^a	109.1 ± 7.81^a	24.7 ± 2.16^a
Mania n = 20	58.6 ± 3.7^b	3.4 ± 5.76^b	132.4 ± 6.50^a	5.86 ± 0.09^b	102.1 ± 5.94	19.3 ± 1.4^b
Paranoid Disorder n = 20	55.1 ± 3.85^b	33.7 ± 6.31^b	137.6 9.94^a	4.58 ± 0.12^a	94.9 ± 5.06	23.2 ± 2.07^a
Control n = 20	66.4 ± 4.06^a	41.6 ± 3.19^a	136.9 ± 8.74^a	4.35 ± 0.07^a	107.1 ± 5.52	21.5 ± 1.25^a

1. n = number of subjects. Triplicate determinations were carried out for each assay.

2. Values carrying different superscripts (a,b,c) vertically are significnatly (P < 0.01) different.

There was a significant ($P < 0.01$) difference in the serum Na^+ level of patients suffering from any of the psychiatric syndromes (Table 3). The serum K^+ concentration was not significantly ($P < 0.01$) affected in the patients suffering from any of the psychiatric syndromes, except in mania and paranoid disorder which were increased. There was no significant change in serum chloride concentration of the patients suffering from any of the psychiatric syndromes, except in mania and paranoid disorder, in which valves were reduced. There was no significant change in the CO_2 content of the patients suffering from any of the psychiatric syndromes (Table 3).

Discussion

Data of the present study indicate that the concentrations of some biogenic amines were significantly affected by psychiatric syndromes. For example, the serum levels of epinephrine were potentiated in patients suffering from schizophrenia, hypomania, mania and paranoid disorders. However, the levels of dopamine and serotonin in patients suffering from all the psychiatric syndromes investigated in the present study were reduced. Norepinephrine levels were elevated in the schizophrenic, hypomanic, manic and paranoid disorder patients.

Wooley and Shaw [19] were the first to suggest that schizophrenia might result from a deficiency in serotoninergic function in the central nervous system (CNS). However, early reports of decreased concentration of 5-HIAA, the major metabolite of 5-HT metabolism were not confirmed by subsequent studies [20,21]. Van praag [22]) and Bondy *et al* [23] previously proposed that depressions are associated with absolute or relative deficiency of biogenic amines in the blood and/or brain, while elation conversely may be associated with an excess of such amines. In the light of this hypothesis, the findings from the present

study succinctly indicate a significant increase in the serum levels of epinephrine and norepinephrine, while the serum levels of dopamine and serotonin decreased in schizophrenic, hypomanic, manic and paranoid disorder patients.

However, it is important that a direct relationship between the concentrations of biogenic amines in the periphery and brain are not likely to exist due to the rate of transport across the blood-brain barrier. But peripheral norepinephrine concentration may indirectly reflect CNS mediated autonomic action [24]. In this regard, Godwin *et al* [25] reported that the norepinephrine level in the cerebrospinal fluid of depressed patients was greater than three times that of non-depressed patients. There is dearth of information in the literature on the relationship between the metabolism of serum biogenic amines and psychiatric disorders.

The elevated serum epinephrine and norepinephrine levels found in the present study may represent a compensatory response to a decrease in adreninergic receptor sites of psychotic patients. Additionally, it is possible that in some psychotic patients, there is an adaptive cardiovascular change due to the elevated serum biogenic amine concentration. Data from the present study suggest that primary increases in peripheral biogenic amines may exist in prolonged anxiety with increased adreninergic activity, and thus could result in changes of emotional states, culminating in psychosis. The relationship of these events, however, is both complicated, uncertain and awaits further research and confirmation.

Serum HIAA concentrations were significantly increased in schizophrenic, hypomaniac, manic and paranoid disorder patients. This may suggest that there is an increase in the rate of catabolism or rate of intra-synaptic inactivation of the biogenic amines in these psychiatric syndromes. These findings may explain why some brain functions medicated by various neuronal systems are altered.

The activities of ALA transaminase and AST transaminase in all the psychiatric syndromes investigated were significantly elevated, except for paranoid disorder, in which AST transaminase activities were reduced. Serum protein concentrations were not affected by schizophrenia and hypomania, but were affected by mania and paranoid disorder. The serum Na^+ and CO_2 levels were not affected by schizophrenia, hypomania, mania and paranoid disorder. Serum K^+ levels were not altered by schizophrenia, hypomania, and paranoid disorder, but were altered by mania. The Cl^- levels were not affected by schizophrenia and hypomania, but were altered by mania and paranoid disorder.

A retention of sodium, particularly of intracellular sodium, in patients with affective disorders suggest a deficiency of the sodium pump or the cell membrane enzyme Na^+, K^+-ATPase, and is intimately involved in the function of the sodium pump. Therefore, it could be implied from the present data that Na^+, K^+-ATPase activity is potentiated by these psychiatric syndromes. Gibbons [26] has indicated that depression is associated with a retention of sodium, while in hypomania, sodium retention was slight or remained in normal range. It has been proposed that some depressed patients have abnormal cell membrane electrolyte transport systems and that these abnormalities may be genetically determined [27].

Gibbons [28] reported a significant decrease in exchangeable sodium upon recovery from depression and mania. There have been a few reports on electrolyte metabolism in affective illness [29], therefore additional studies are necessary to establish if there is any relationship.

Serum or blood constituents have been reported as increased, decreased or normal in schizophrenia, but generally the results have not been consistent [30]. In addition, several serum enzyme changes and abnormal liver function tests have been reported in schizophrenia with some inconsistent findings.

The principal condition in which level of serum activity of ALA transaminase is elevated is liver disease, especially with liver cell damage, while that of AST transaminase in myocardial infarction and liver disease, especially with liver cell damage [31]. The assay of serum enzymes is used as an important aid to diagnosis. The level of activity of a number of enzymes is raised in different pathological conditions.

In protein energy malnutrition, serum albumin and proteins are used as growth parameters [13]. For instance, serum albumin concentration is low, owing to a failure of synthesis in the liver, while a potassium deficiency arises due to diarrhea, but plasma Na^+ is usually normal. In the present study from the data obtained for the serum proteins, it clearly confirms that the psychiatric patients and controls used in this study were not malnourished. Neurological complications of liver disease often take the form of intermittent confusion and abnormal behaviour, associated with a curious flapping, or wing-beating, tremor of the hands (asterixis) [29]. Therefore, in any patient presenting with such symptoms, it is necessary to carry out a battery of liver function tests, including assay of ALA and AST transaminase activities.

Human brain tissue is hardly available for direct biochemical analysis, therefore different indirect approaches, using blood or cerebrospinal fluid or urine, are used to evaluate the central serotoninergic and adreninergic metabolism in man. For example, serotonin uptake by blood platelets has been used as an indirect measure of the rate of serotonin intrasynaptic inactivation, since serotonin transport through the presynaptic membrane and through the external membrane of blood platelets have similar kinetic characteristics [32] and show similar susceptibility to activity and inhibitory effects [33]. In addition, serotonin uptake by blood platelets has been used as an indirect measure of the rate of serotonin re-uptake by presynaptic nerve endings and as rate of serotonin intrasynaptic inactivation in depressed patients [34], and in malnourished rats [35].

Therefore, the present study is another indirect attempt to evaluate the central nervous system using serum biogenic amines, protein and electrolytes, to unravel whether they are affected by psychiatric syndromes. Our findings indicate that dopamine and serotonin levels were curtailed, while norepinephrine and epinephrine levels were elevated by schizophrenia, hypomania, mania and paranoid disorder. Additionally, data obtained for serum enzymes, protein and electrolytes contribute information, which will be useful in biological psychiatry.

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