Impact of Lead Toxicity on Brain Metabolisms of Nucleic Acid and Catecholamine in Protein Malnourished Rats

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Summary The brain biochemistry in terms of certain key substances of brain were studied in 18% protein and 6% protein-fed rats following lead ingestion at a level of 1% in the diet. Lead ingestion diminished the protein and increased the RNA content of brain, and, consequently reduced the protein/RNA ratio. The RNA/DNA ratio in brain was elevated in lead toxicity, while the protein/DNA ratio remained unaltered. The RNase and DNase activities of brain were decreased. Lead treatment diminished the glutathione (GSH) level of blood but the GSH level of brain was not altered significantly by the lead treatment. The plasma protein level was also diminished after lead treatment. The effects of lead on some of these parameters were found to be more pronounced in rats receiving the 6% protein diet. The serotonin (5-HT) level of brain was reduced, while the norepinephrine (NE) and dopamine (DA) levels of brain were elevated following lead treatment. The monoamine oxidase (MAO) and tryptophan hydroxylase (TPH) activities and 5-hydroxyindole acetic acid (5-HIAA) content of brain were elevated in lead-ingested rats. The effects of lead on these parameters were found to be potentiated when the rats were fed on a 6% protein diet. These studies suggest that lead at the present dose affects brain biochemistry in terms of both nucleic acids and amine metabolism, and protein deficiency potentiates some of these lead-induced changes.

Key Words lead toxicity, protein deficiency, brain, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), RNase, DNase, blood, GSH, plasma protein, serotonin (5-HT), norepinephrine (NE), dopamine (DA), monoamine oxidase (MAO), tryptophan hydroxylase (TPH), 5-hydroxyindole acetic acid (HIAA)

Lead poisoning is well recognized in man and domestic animals (1–4), as it is widely distributed in the environment. Anemia and disorders of porphyrin metabolism are characteristics of lead poisoning (1). In addition to anemia, lead
poisoning in animals and man causes fatigue, headache, weight loss and chronic renal diseases accompanied by proteinuria, aminoaciduria and hyperuricemia (1). Lead-induced neurological effects are also well documented. Thus it was demonstrated that lead affected the central nervous system and produced behavioral abnormalities in children (5-7). Lead toxicity in young growing rats was found to induce hyperactivity, aggressiveness and behavioral alterations (8-10). Hyperactivity and behavioral disturbances were also noted in lead-poisoned mice (11) and monkeys (12, 13). Symptoms of mental retardation and cerebral atrophy were also recognized in children following exposure to lead (14). These studies indicate, therefore, that lead might affect the key substances of the brain subserving its functions. Again, protein deficiency affects development and functions of brain (15-17) and also influences the toxicity of drugs and other substances (18, 19).

It is, therefore, worthwhile to study the impact of lead toxicity on brain in terms of certain key substances of brain such as nucleic acids, amines, glutathione, etc., on an adequate and inadequate protein status, and accordingly, the present investigation was undertaken.

MATERIALS AND METHODS

Animals and diets. Male albino rats of Wistar strain weighing 60-80g were divided into four groups of equal average body weight. The animals of half of the groups were fed on the diet containing 18% protein (casein) while those of the remaining groups were fed on the diet containing 6% protein (casein). The carbohydrate (amyloam) contents of the above two diets were kept at 71% and 83%, respectively. The other ingredients of the diets and the supply of vitamins were the same as reported elsewhere (20, 21). Some of the rats from each of the dietary regimens received 1% lead acetate in the diet. The animals were maintained on these diets for 21 days. The animals of control groups were pair-fed with those of lead-treated groups.

Removal of blood and brain. The animals were fasted overnight before they were sacrificed by decerebration. Blood was collected in an oxalated syringe from the portal vein. The brains were dissected immediately and frozen after wiping off of the blood with filter paper and weighing. A portion of the blood was centrifuged for separation of plasma.

Analysis. Brain samples were digested in nitric acid in a boiling waterbath. Lead contents of these samples and blood were determined by the method of Berman (22) using atomic absorption spectrophotometry. Glutathione (GSH) of blood and brain tissue was assayed according to Grunert and Phillips (23). The total protein content of plasma and brain tissue was estimated by the biuret reagent (24).

Determination of RNA and DNA. RNA and DNA contents of the brain tissue were measured by the method of Munro and Fleck (25) except that DNA was extracted with 0.8 M perchloric acid at 70°C and determined colorimetrically by the
diphenylamine method as modified by Giles and Meyers (26).

Measurement of RNase and DNase activities. RNase activity of the brain tissue was determined by the method as employed elsewhere (27), while the DNase activity was assayed according to McDonald (28).

Extraction and determination of 5-HT, NE and DA. Serotonin (5-HT), norepinephrine (NE) and dopamine (DA) were extracted from the brain according to the method of Sadavongvivad (29) with slight modification. The brain tissue was homogenized in acidified butanol at 4°C. After centrifugation at 4°C, butanol extract was collected and a portion of butanol extract was processed for fluorescent development (29) and the fluorescence of 5-HT was measured using a Perkin-Elmer MPF 448 Fluorescence Spectrophotometer with the activation wavelength set at 295 nm and the emission wavelength at 550 nm as adapted by Udenfriend, Weisbach and Brodie (30).

Another portion of the butanol extract was shaken with 0.1 M phosphate buffer, pH 6.5, and the aqueous layer containing the NE and DA separated out by centrifugation. A definite portion of the aqueous layer was then processed (29) for development of fluorophores of NE and DA. The fluorescence of NE was read with the activation wavelength at 385 nm and emission wavelength at 485 nm. The fluorescence of DA was measured at an activation wavelength of 320 nm and emission wavelength of 370 nm.

Assay of tryptophan hydroxylase (TPH) activity. The brain tissue was homogenized 1:3 (w/v) at 4°C in 0.05 M Tris-acetate, pH 7.6, containing 10^{-3} M 2-mercaptoethanol. The supernatant obtained after spinning the homogenate at 30,000×g for 45 min in a preparative ultracentrifuge (Beckman Model L3-50) at 2-4°C was used for assaying the TPH activity according to the method of Gal and Patterson (31). The incubation mixture in a total volume of 2 ml contained 50 mM Tris-acetate, pH 7.6, 0.16 mM L-tryptophan, 20 μg catalase and 0.2 ml of brain 30,000×g supernatant as enzyme source.

Assay of monoamine oxidase (MAO) activity. The brain was homogenized in 0.25 M sucrose containing 0.1 M phosphate buffer, pH 7.4, at 2-4°C. The MAO activity in the homogenate was assayed by the method of Green and Haughton (32).

Determination of 5-hydroxyindole acetic acid (5-HIAA). The 5-HIAA content of brain was measured according to the method suggested by Udenfriend, Weisbach and Brodie (30).

RESULTS

The data presented in Table 1 indicate that lead treatment decreased slightly the body weight of rats receiving either the 18% or 6% protein diet but the changes were not statistically significant. On the other hand, there was a slight increase (statistically significant) in the brain weight of rats fed on either the 18% or 6% protein diet. It is revealed from the Table 2 that lead toxicity diminished the GSH
Table 1. Effect of lead on body and brain weights. (The values are means±SEM)

<table>
<thead>
<tr>
<th>Groups of animals</th>
<th>Body weight (g)</th>
<th>Brain weight (g)</th>
<th>Brain weight g/100 g body weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>18% Protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>122.9±1.91</td>
<td>1.65±0.07</td>
<td>1.34±0.08</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>118.7±2.66</td>
<td>1.95±0.06</td>
<td>1.64±0.06</td>
</tr>
<tr>
<td></td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.02</td>
</tr>
<tr>
<td>6% Protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>107.8±2.83</td>
<td>1.53±0.08</td>
<td>1.42±0.09</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>100.1±2.59</td>
<td>1.88±0.06</td>
<td>1.87±0.08</td>
</tr>
<tr>
<td></td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

The figures in the parentheses indicate the number of animals.

Table 2. Effect of lead on plasma protein, and glutathione and lead levels of blood and brain. (The values are means±SEM)

<table>
<thead>
<tr>
<th>Groups of animals</th>
<th>Plasma protein (g/100 ml)</th>
<th>Brain Glutathione (mg/100 g wet weight)</th>
<th>Blood Glutathione (mg/100 ml)</th>
<th>Lead levels Blood (µg/100 ml)</th>
<th>Lead levels Brain (µg/g wet weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>6.0±0.14</td>
<td>90.6±2.9</td>
<td>46.7±3.5</td>
<td>18.5±1.3</td>
<td>0.85±0.08</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>5.3±0.18</td>
<td>95.4±2.9</td>
<td>33.8±4.4</td>
<td>35.6±1.8</td>
<td>2.92±0.35</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>6% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>5.2±0.19</td>
<td>80.6±2.7</td>
<td>42.4±2.5</td>
<td>16.7±1.4</td>
<td>0.74±0.06</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>4.4±0.16</td>
<td>87.2±2.7</td>
<td>28.3±3.3</td>
<td>39.0±1.9</td>
<td>3.14±0.42</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.01</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.01</td>
</tr>
</tbody>
</table>

The figures in the parentheses indicate the number of animals.

Level in blood but the GSH content of brain was not significantly altered by lead ingestion. This change in GSH level of blood was found to be more in rats when fed on a 6% protein diet than when fed on an 18% protein diet. The plasma protein level was also diminished after lead treatment and the percentage decrease was slightly more in rats fed on the 6% protein diet than when fed on the 18% protein diet.

It is further revealed from Table 2 that lead levels of blood and brain were elevated significantly by lead ingestion, and this effect particularly on brain lead level was more on a 6% protein diet than on an 18% protein diet.

The results depicted in Table 3 reveal that lead ingestion diminished the protein content and increased the RNA content of brain. Protein/RNA ratio was
Table 3. Effect of lead ingestion on brain protein, nucleic acids and nucleases. (The values are means±SEM)

<table>
<thead>
<tr>
<th>Groups of animals</th>
<th>µg RNA/ mg protein</th>
<th>Protein (g/100g tissue)</th>
<th>RNA (mg/100g tissue)</th>
<th>Protein/ RNA ratio</th>
<th>DNA (mg/100g tissue)</th>
<th>Protein/ DNA ratio</th>
<th>RNA/ DNA ratio</th>
<th>RNase (mg/100g tissue)</th>
<th>DNase (mg/100g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>18.8±0.5</td>
<td>11.2±0.1</td>
<td>210.0±12.0</td>
<td>53.3±4.2</td>
<td>154.0±8.0</td>
<td>72.7±2.8</td>
<td>1.36±0.16</td>
<td>116.0±8.9</td>
<td>27.5±1.1</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>20.8±0.5</td>
<td>10.8±0.1</td>
<td>255.0±11.0</td>
<td>42.0±3.9</td>
<td>140.0±7.0</td>
<td>76.8±3.6</td>
<td>1.82±0.12</td>
<td>86.4±5.1</td>
<td>22.0±1.6</td>
</tr>
<tr>
<td>p &lt; 0.02</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>6% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>17.6±0.6</td>
<td>9.62±0.02</td>
<td>179.0±10.0</td>
<td>53.8±3.8</td>
<td>151.0±8.0</td>
<td>63.8±4.2</td>
<td>1.18±0.1</td>
<td>123.0±8.0</td>
<td>30.0±3.9</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>21.3±0.5</td>
<td>8.84±0.16</td>
<td>233.0±12.0</td>
<td>38.0±3.4</td>
<td>131.0±8.0</td>
<td>67.7±5.8</td>
<td>1.78±0.2</td>
<td>80.4±7.2</td>
<td>15.9±2.8</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.02</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.02</td>
</tr>
</tbody>
</table>

The figures in the parentheses indicate the number of animals.

Table 4. Effect of lead ingestion on brain monoamines, hydroxyindole acetic acid and certain related enzyme activities. (The values are means±SEM)

<table>
<thead>
<tr>
<th>Groups of animals</th>
<th>5-Hydroxytryptamine* (5-HT)</th>
<th>Noradrenaline* (NE)</th>
<th>Dopamine* (DA)</th>
<th>Monoamine oxidase (MAO) activity**</th>
<th>Hydroxyindole acetic acid* (HIAA)</th>
<th>Tryptophan hydroxylase activity†</th>
</tr>
</thead>
<tbody>
<tr>
<td>18% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>0.70±0.02</td>
<td>0.46±0.03</td>
<td>0.44±0.02</td>
<td>4.51±0.19</td>
<td>0.52±0.05</td>
<td>3.25±0.17</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>0.62±0.01</td>
<td>0.60±0.03</td>
<td>0.52±0.03</td>
<td>5.20±0.22</td>
<td>0.67±0.02</td>
<td>3.97±0.10</td>
</tr>
<tr>
<td>p &lt; 0.02</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>6% Protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pair-fed control (6)</td>
<td>0.77±0.03</td>
<td>0.44±0.02</td>
<td>0.45±0.01</td>
<td>4.48±0.11</td>
<td>0.48±0.02</td>
<td>2.83±0.13</td>
</tr>
<tr>
<td>Lead-treated (7)</td>
<td>0.62±0.02</td>
<td>0.56±0.03</td>
<td>0.56±0.04</td>
<td>5.54±0.29</td>
<td>0.72±0.04</td>
<td>3.81±0.14</td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.001</td>
</tr>
</tbody>
</table>

The figures in the parentheses indicate the number of animals. *µg/g wet brain tissue. **Units/mg protein/30 min. †nmole of 5-hydroxyindoles formed/mg protein/h.
accordingly reduced in lead-ingested rats. The effects of lead on these parameters were found to be more pronounced when the rats were fed on a 6% protein diet. The DNA content of brain was not significantly altered by lead ingestion. While the protein/DNA ratio was not significantly altered, the RNA/DNA ratio in the brain was elevated in lead toxicity. The percentage increase in brain RNA/DNA ratio due to lead ingestion was more on a 6% protein diet than on an 18% protein diet. It is further seen from the Table 3 that lead ingestion decreased the brain RNase and DNase activities, and the extent of decrease was more marked on a 6% protein diet.

Lead-treated rats exhibited decreased 5-HT and increased NE and DA contents in the brain (Table 4). This effect of lead was more marked on a 6% protein diet. The MAO activity, TPH activity and 5-HIAA content of brain were elevated in lead-ingested rats. The effects of lead on these parameters were found to be more pronounced when the rats were fed on a 6% protein diet.

DISCUSSION

The slight fall in body weight following lead ingestion was not found to be statistically significant but slight enlargement of the brain (increase in weight per 100 g body weight) under the same condition was found to be statistically significant. The effect of lead in increasing the size of the various organs, such as liver and kidney, was demonstrated (2). Slight enlargement of the brain following lead intoxication was also noted earlier (4). The increase in size might be due to accumulation of lead in this soft tissue (33). The impact of lead in increasing the size of the brain was comparable between the groups of rats receiving the 18% and 6% protein diet. This demonstrates that the effect of the present dose of lead on brain weight is independent of dietary level of protein. Although the change in brain glutathione level following ingestion of the present dose of lead was not statistically significant, there is a tendency of the brain tissue to show enhanced glutathione level. A significant elevation in the glutathione level in other organs, such as liver and kidney, following lead treatment was demonstrated and this was attributed to the increased synthesis of glutathione as a compensatory mechanism to overcome the toxicity of lead (4). It is, therefore, possible that the brain tissue following ingestion of the present dose of lead develops also a tendency to maintain an elevated concentration of glutathione. The diminished concentration of blood glutathione level in the present condition may be ascribed to increased glutathione conjugation. Such binding of glutathione with metals including lead was also demonstrated (34).

Lead-treated animals showed diminished plasma protein levels. This decrease in plasma protein level following lead intoxication was more in protein-malnourished rats, indicating the potentiation of toxic effect of lead on plasma protein level by protein deficiency. The decrease in plasma protein level following lead intoxication may be ascribed to reduced synthesis of plasma proteins by the
liver as evident from the fact that lead administration impaired the binding of phenylalanyl and lysyl-tRNA to ribosome (1) and the incorporation of $^{14}$C-amino acid into liver proteins (3).

There was a slight but significant decrease in the protein content of the brain tissue following lead ingestion and the percentage decrease appeared to be a little more on a 6% protein diet than on an 18% protein diet. This indicates that the protein-depleting effect of lead on brain is aggravated by lowering the protein content of the diet. Although there was a fall in protein content of the brain, the protein/DNA ratio was not significantly altered following lead ingestion. This suggests that cellular protein concentration of brain remains unaltered. It was demonstrated earlier that lead treatment reduced the binding of phenylalanyl and lysyl-tRNA to ribosome (1) and diminished the incorporation of $^{14}$C-amino acid into liver protein (3). Lead-induced inhibition of $^{14}$C-amino acid incorporation into *E. coli* amino-acyl-tRNA was also noticed by Ulmer and Vallee (1). Further studies revealed that lead caused a marked disaggregation of polyribosomes (1). So, it is possible that lead ingestion in the present investigation might reduce the protein synthesis in brain and, accordingly, unaltered protein/DNA ratio in lead intoxication might suggest diminished breakdown accompanying reduced synthesis of brain protein. There are evidences suggesting utilization of energy in the form of ATP in the catabolism of proteins (35). On the other hand, it was demonstrated that lead hydrolyzes ATP non-enzymatically (1) and retards cell respiration and oxidative phosphorylation (1) and, consequently, might limit the availability of ATP. So, it is conceivable that lead ingestion might reduce the breakdown of tissue proteins. This contention might be supported by the fact that lead treatment diminished the activity of tissue aminopeptidase (36), indicating that lead might affect the enzyme systems associated with the breakdown of tissue proteins.

The increased RNA content of brain after lead treatment (Table 3) also led to an elevation in RNA/DNA ratio in the brain, suggesting an enhanced cellular RNA concentration. These changes following lead treatment were found to be more marked on a low protein (6% protein) diet. This indicates that the action of lead on brain RNA is potentiated by the low protein diet. The increased cellular RNA concentration might arise from enhanced synthesis or diminished breakdown of RNA or due to both mechanisms. The decreased brain RNase activity following lead treatment suggests that the reduced degradation of RNA might be a factor for enhanced cellular RNA concentration in lead intoxication. Decreased RNase activity following lead treatment was also demonstrated in other tissues (37).

The $\mu$g RNA/mg protein which is a measure of protein synthesizing capability was elevated in brain following lead ingestion. This indicates that, although there was a decreased rate of protein synthesis in brain following lead ingestion, the increased capacity for protein synthesis might be of importance from the point of view of adaptive response of the brain to lead intoxication.

Following lead treatment, DNase activity was found to be decreased but DNA concentration was not altered significantly. So, there might be a possibility of
reduced synthesis of DNA in addition to reduced breakdown of DNA. The reduction in the rate of breakdown of DNA in lead-treated animals might be considered as an adaptive mechanism to conserve total DNA level in the vital tissues, such as brain.

It has been presumed that lead inhibited most of the enzymes by binding single functional-SH group (1). Whether lead inhibits RNase and DNase by binding with functional-SH group is to be ascertained by further studies.

Lead toxicity at the present dose also appears to influence the brain functions in terms of monoamine changes. Chronic exposure of children to lead was found to be associated with behavioral disorders, learning disabilities and mental retardation (38-40). Animal studies also demonstrated that chronic perinatal low level of lead exposure produced alterations of both learned and spontaneous behavioral patterns (10, 11, 41-44). Rat pups chronically exposed to lead demonstrated locomotor hyperactivity (45). Lead-treated mice were also shown to exhibit hyperactivity (11). On the other hand, behavioral stimulation or excitation in a number of situations was found to be associated with increased brain levels of NE and DA (46). Accordingly, the increased levels of NE and DA contents of brain following lead treatment, as noted in the present investigation, are in conformity with the above observations. The reduced brain 5-HT level following lead treatment suggests that the changes in 5-HT levels are opposite to those of catecholamines, suggesting a reciprocal interaction between serotonergic and catecholaminergic neurons. Such reciprocal interaction was also demonstrated by Komulainen, Pietarinen and Tuomisto (47). Lead-induced changes in brain 5-HT and DA levels were more marked when the rats were maintained on a low protein diet (Table 4). Tandon, Flora and Singh (48) also reported lead-induced alterations in brain monoamine levels to be more marked in nutritional deficiency, such as vitamin B-complex deficiency.

Lead treatment enhanced the MAO activity. Accordingly, the diminished brain 5-HT level following lead intoxication may be ascribed to increased catabolism of 5-HT. That this is possible becomes evident from the increased hydroxyindole acetic acid (HIAA) level in brain following lead treatment. The report of increased urinary excretion of biogenic metabolites in lead-exposed persons (49) also conforms to the present observation. The lead-induced changes in MAO activity and HIAA level were found to be more marked in protein deficiency, and, consequently, this can account for the more marked reduction of brain 5-HT level when lead treatment was accompanied by protein deficiency. Contrary to the reduced 5-HT level, the tryptophan hydroxylase (TPH) activity in the brain was elevated after lead treatment. The percentage increase in the activity of TPH was also more in the lead-treated protein-deficient rats (Table 4). It is likely that this increase in TPH activity may be an adaptive response to the reduced level of 5-HT in brain in an attempt to compensate for increased breakdown of 5-HT in lead intoxication. But, the increased TPH activity so observed was probably not sufficiently large enough to overcome the enhanced quantum of MAO activity, and,
accordingly, there was reduced brain 5-HT level in lead intoxication in spite of stimulated TPH activity. Similar adaptive response of TPH to diminished level of 5-HT was also noted in certain other altered nutritional conditions (50, 51). It was noted that adrenalectomy of newborn rats enhanced the MAO activity, and also blocking of glucocorticoid biosynthesis in 8-week-old rats by metopirone administration increased the MAO activity (52). On the other hand, there are some reports of adrenocortical suppression in lead intoxication (53). It is, therefore, plausible that enhanced MAO activity following lead ingestion might result from adrenocortical insufficiency.

Lead was also found to increase the uptake of tyrosine, the precursor of catecholamines, by the brain, as evidenced by enhanced uptake of tyrosine by rat brain synaptosomes (54). Enhanced uptake of tyrosine was also described in tissue prepared from lead-exposed mice (55). Therefore, it is possible that increased NE and DA contents of brain following lead exposure might result from enhanced rate of synthesis due to increased availability of substrate.

It appears, therefore, that lead treatment at the present dose alters the nucleic acid and amine metabolism of brain and some of these alterations could be ascribed to the changes in some of the associated enzyme activities. It is further revealed that some of the lead-induced metabolic changes in brain are potentiated by the protein deficiency of the animal.

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Vol. 38, No. 5, 1992


