Dietary protein restriction causes modification in aluminum-induced alteration in glutamate and GABA system of rat brain

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Abstract

Background: Alteration of glutamate and γ-aminobutyrate system have been reported to be associated with neurodegenerative disorders and have been postulated to be involved in aluminum-induced neurotoxicity as well. Aluminum, an well known and commonly exposed neurotoxin, was found to alter glutamate and γ-aminobutyrate levels as well as activities of associated enzymes with regional specificity. Protein malnutrition also reported to alter glutamate level and some of its metabolic enzymes. Thus the region-wise study of levels of brain glutamate and γ-aminobutyrate system in protein adequacy and inadequacy may be worthwhile to understand the mechanism of aluminum-induced neurotoxicity.

Results: Protein restriction does not have any significant impact on regional aluminum and γ-aminobutyrate contents of rat brain. Significant interaction of dietary protein restriction and aluminum intoxication to alter regional brain glutamate level was observed in the tested brain regions except cerebellum. Alteration in glutamate α-decarboxylase and γ-aminobutyrate transaminase activities were found to be significantly influenced by interaction of aluminum intoxication and dietary protein restriction in all the tested brain regions. In case of regional brain succinic semialdehyde content, this interaction was significant only in cerebrum and thalamic area.

Conclusion: The alterations of regional brain glutamate and γ-aminobutyrate levels by aluminum are region specific as well as dependent on dietary protein intake. The impact of aluminum exposure on the metabolism of these amino acid neurotransmitters are also influenced by dietary protein level. Thus, modification of dietary protein level or manipulation of the brain amino acid homeostasis by any other means may be an useful tool to find out a path to restrict amino acid neurotransmitter alterations in aluminum-associated neurodisorders.

Background

The neurotoxic effect of aluminum is well documented [1–3] and have been implicated in several chronic neurodisorders, namely, Alzheimer’s disease, amyotropic lateral sclerosis, dialysis encephalopathy, Parkinson’s disease, demential complex of Guam, etc. [3,4]. The adverse effects of aluminum are manifested in impairment of higher order functions of brain [5,6]. Development of higher brain functions is also impaired by nutritional protein insufficiency [7,8]. Augmented brain glutamate level is observed in protein malnutrition [9] as well as in aluminum intoxication [10]. Aluminum-induced alteration in specific
enzyme activity and cellular components is observed to be partially refrained in protein malnutrition [11,12], which suggests the involvement of the common factor, glutamate. Thus alteration in brain glutamate metabolism may play significant role in aluminum-induced higher function disorders of brain.

On the other hand, prolonged malnutrition leads to a substantial, but reversible, reduction in the cholinergic innervation of the hippocampal formation and to an irreversible loss of hippocampal cholinergic and GABAergic neurons [13]. The hippocampus is also recognized to be the most sensitive area for aluminum intoxication [14]. The acclaimed idea that the diet can alter brain neurochemistry has been experienced once again and the present investigation is undertaken to study the impact of aluminum on the brain glutamate and GABA systems in a condition where the brain glutamate level is pre-elevated through protein malnutrition.

**Results**

**Body weight and food intake of animals**

Changes in the difference between body weights of aluminum treated (BW_T) and pair-fed control (BW_C) animals during the period of treatment have been depicted in figure 1. Figure 2 shows the changes in food intake in aluminum treated groups of animals, of both adequate protein and restricted protein diet regimens, during the period of treatment.

**Regional aluminum content of brain**

Regionwise aluminum contents of brain in different groups of rats are presented in table 1. Following aluminum treatment of rats fed on an adequate protein diet, the increases in the aluminum contents of the cerebrum, thalamic area, midbrain-hippocampal region and cerebellum were 52%, 69%, 100% and 50% respectively, while on an inadequate protein diet such increases in the respective brain regions were 85%, 80%, 89% and 73%. Though there is significant amount of added components for treatment effects in all the tested brain regions, Scheffe’s F test for multiple comparisons showed that aluminum exposure significantly increased the aluminum content of cerebrum, thalamic area and midbrain-hippocampal region of both the dietary regimens. However, two factor ANOVA (with replication) showed that only effects of aluminum treatment were significant in all the four brain regions (Table 1).

**Regional glutamate content of brain**

Table 2 shows changes in glutamate content in different regions of brain on exposure to aluminum. Single factor ANOVA was found to be significant in all the tested brain regions. Scheffe’s F test for multiple comparisons indicates that in rats maintained on an adequate-protein diet, glutamate level of cerebrum (23%), thalamic area (33%), and cerebellum (34%) were insignificantly increased whereas in midbrain-hippocampal region the glutamate level is significantly increased (45%). On the other hand, decreases in cerebrum (41%) and thalamic area (41%), and increase (36%) in cerebellum of rats maintained on a low-protein diet were found to be significant by Scheffe’s F test for multiple comparisons. Two factor ANOVA with replication showed that aluminum exposure contributed significantly to the changes of the glutamate levels in all...
the tested brain regions except the thalamic area. Similarly, protein restriction contributed significantly to the alterations of thalamic area and cerebellum. Interactions of dietary protein deficiency and aluminum exposure were, however, significant in cerebrum, thalamic area and midbrain-hippocampal region.

**Regional glutamate-α-decarboxylase activity of brain**

The changes in glutamate-α-decarboxylase (GAD) activities in response to aluminum exposure in different regions of brain are shown in table 3. Significant impact of the present treatment was observed in GAD activities of all the tested brain regions, except thalamic area. Cerebellum of the rats maintained on adequate protein diet did not show any significant alterations (Scheffe’s F test for multiple comparisons). Significant increases were observed in specific brain regions (cerebrum 43% and midbrain-hippocampal region 36%) of the adequately protein-fed group however, significant decreases were observed in all the tested brain regions (cerebrum : 24%, midbrain-hippocampal region : 12% and cerebellum : 27%) except thalamic area of the rats fed with a protein-restricted diet. Two factor ANOVA with replication showed that aluminum exposure and protein restriction contributed significantly with the changes of the GAD activity of cerebrum and midbrain-hippocampal regions only, although, the interactions of impact of dietary protein deficiency and

### Table 1: Regional aluminum (µmoles / 100 mg wet tissue) contents of brain.

| Brain regions            | Groups of animals | Statistical calculation (F) |
|--------------------------|-------------------|------------------------------|
|                          | Normal protein    | Low protein                 | ANOVA Single factor | ANOVA Two factors (with replication) |
|                          | Control           | Aluminum exposed            | Control            | Aluminum exposed | Protein | Aluminum | Interaction | Protein | Aluminum | Interaction |
| Cerebrum                 | 2.72 ± 0.39       | 4.13 ± 0.38                 | 2.50 ± 0.41        | 4.62 ± 0.47      | 6.29     | 0.11     | 18.04      | 0.73    |          |
| Thalamic area            | 4.87 ± 0.82       | 8.24 ± 0.40                 | 4.50 ± 0.62        | 8.08 ± 0.57      | 10.49    | 0.17     | 31.28      | 0.03    |          |
| Midbrain-hippocampal     | 4.52 ± 0.76       | 9.02 ± 0.69 *               | 4.40 ± 0.65        | 8.33 ± 0.92      | 10.40    | 0.28     | 30.78      | 0.14    |          |
| region                   | 2.52 ± 0.46       | 3.77 ± 0.22                 | 2.32 ± 0.44        | 4.02 ± 0.52      | 4.13     |          | 0.00       | 12.10   |          |

Data are means of six observations ± SEM. * indicates significant difference (p < 0.05) in comparison to respective control. # indicates calculated F is higher than the critical F (α = 0.05).

### Table 2: Regional glutamate contents (µmoles / g wet tissue) of brain.

| Brain regions            | Groups of animals | Statistical calculation (F) |
|--------------------------|-------------------|------------------------------|
|                          | Normal protein    | Low protein                 | ANOVA Single factor | ANOVA Two factors (with replication) |
|                          | Control           | Aluminum exposed            | Control            | Aluminum exposed | Protein | Aluminum | Interaction | Protein | Aluminum | Interaction |
| Cerebrum                 | 5.75 ± 0.41       | 7.10 ± 0.47                 | 9.03 ± 0.56        | 5.35 ± 0.25      | 14.38    | 3.06     | 7.09       | 32.98   |          |
| Thalamic area            | 5.92 ± 0.34       | 7.88 ± 0.72                 | 7.02 ± 0.52        | 4.15 ± 0.31      | 10.30    | 6.89     | 0.80       | 23.21   |          |
| Midbrain-hippocampal     | 5.88 ± 0.37       | 8.50 ± 0.56 *               | 7.05 ± 0.38        | 6.28 ± 0.22      | 8.24     | 1.72     | 5.25       | 17.75   |          |
| region                   | 4.92 ± 0.44       | 6.48 ± 0.43                 | 5.63 ± 0.21        | 7.68 ± 0.40      | 9.79     | 6.35     | 22.61      | 4.98    |          |

Data are means of six observations ± SEM. * indicates significant difference (p < 0.05) in comparison to respective control. # indicates calculated F is higher than the critical F (α = 0.05).
aluminum exposure were significant in all the tested brain regions.

**Regional γ-aminobutyrate content of brain**
Table 4 represents the changes in regional γ-aminobutyrate (GABA) contents of different brain regions of both adequate and inadequate protein diet regimens as a result of aluminum insult. In most of the tested brain regions the GABA levels were found to be altered insignificantly. However, significant increment in the GABA content of cerebellum of the protein restricted group was observed in response to aluminum exposure.

**Table 3: Regional GAD activity (µmoles of GABA produced / hr / mg wet tissue) of brain.**

| Brain regions      | Groups of animals | Statistical calculation (F) |
|--------------------|-------------------|----------------------------|
|                    | Normal protein    | Low protein                |
|                    | ANOVA             | ANOVA Two factors          |
|                    | Control           | Aluminum exposed           |
|                    | Control           | Aluminum exposed           |
| Cerebrum           | 30.91 ± 2.18      | 57.67 ± 1.62 *             |
|                    | 41.65 ± 2.60      | 31.47 ± 1.55 *             |
|                    | 37.93 *           | 14.48 # Aluminum : 13.68 # |
|                    |                   | 82.63 # Interaction :      |
|                    |                   | 4.77 # Interaction :       |
|                    |                   | 20.27 #                   |
|                    |                   | Protein : 14.48 #          |
|                    |                   | Aluminum : 13.68 #         |
|                    |                   | Interaction : 82.63 #      |
|                    |                   | Protein : 13.68 #          |
|                    |                   | Interaction : 4.77 #       |
|                    |                   | Interaction : 20.27 #      |
|                    |                   | Protein : 14.48 #          |
|                    |                   | Aluminum : 13.68 #         |
|                    |                   | Interaction : 82.63 #      |
|                    |                   | Protein : 14.48 #          |
|                    |                   | Interaction : 4.77 #       |
|                    |                   | Interaction : 20.27 #      |
|                    |                   | Protein : 14.48 #          |
|                    |                   | Interaction : 4.77 #       |
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|                    |                   | Interaction : 4.77 #       |
|                    |                   | Interaction : 20.27 #      |
|                    |                   | Protein : 14.48 #          |
|                    |                   | Interaction : 4.77 #       |
|                    |                   | Interaction : 20.27 #      |

Data are means of six observations ± SEM. * indicates significant difference (p < 0.05) in comparison to respective control. # indicates calculated F is higher than the critical F (α = 0.05).

**Table 4: Regional GABA contents (µmoles / g wet tissue) of brain.**

| Brain regions      | Groups of animals | Statistical calculation (F) |
|--------------------|-------------------|----------------------------|
|                    | Normal protein    | Low protein                |
|                    | ANOVA             | ANOVA Two factors          |
|                    | Control           | Aluminum exposed           |
|                    | Control           | Aluminum exposed           |
| Cerebrum           | 2.82 ± 0.21       | 3.05 ± 0.41                |
|                    | 3.50 ± 0.24       | 3.05 ± 0.25                |
|                    | 0.99              | Protein : 1.42 Aluminum : 0.14 |
|                    |                   | Interaction : 1.42         |
|                    |                   | Protein : 0.01 Aluminum : 2.48 |
|                    |                   | Interaction : 1.80         |
|                    |                   | Protein : 0.13 Aluminum : 0.17 |
|                    |                   | Interaction : 0.00         |
|                    |                   | Protein : 0.03 Aluminum : 11.41 # |
|                    |                   | Interaction : 2.26         |
|                    |                   | Protein : 0.03 Aluminum : 11.41 # |
|                    |                   | Interaction : 2.26         |
|                    |                   | Protein : 0.03 Aluminum : 11.41 # |
|                    |                   | Interaction : 2.26         |

Data are means of six observations ± SEM. * indicates significant difference (p < 0.05) in comparison to respective control. # indicates calculated F is higher than the critical F (α = 0.05).

Regional γ-aminobutyrate transaminase activity of brain
The alterations in γ-aminobutyric acid transaminase (GABA-T) activities are presented in table 5. In response to aluminum exposure the GABA-T activities were found to be decreased in cerebrum (27%), thalamic area (51%) and cerebellum (42%) whereas increased in midbrain-hippocampal region (74%) of the adequately protein-fed group. The GABA-T activity was found to be increased in cerebrum (79%), thalamic area (9%) and cerebellum (11%) and decreased in midbrain-hippocampal region (50%) when the inadequately protein-fed group was exposed to aluminum. Though there is significant amount of added components for treatment effects in all the tested brain regions, Scheffe’s F test for multiple comparisons
showed that alterations in thalamic area and midbrain-hippocampal region of normal protein-fed group and cerebrum and midbrain-hippocampal region of restricted protein-fed group are only significant. Two factor ANOVA with replication showed that aluminum exposure and protein restriction contributed significantly on the changes of the GABA-T activity of only thalamic area and cerebellum, respectively. However, the interactions of impact of dietary protein deficiency and aluminum exposure were significant in all the tested brain regions.

Regional succinic semialdehyde content of brain
Table 6 shows the alterations in regional succinic semialdehyde (SSA) content in response to aluminum treatment. No significant alteration in SSA content (Scheffe’s F test for multiple comparisons) was observed in any of the tested brain regions of rats maintained on low protein diet. Similarly no significant contribution was imparted by protein restriction in any brain region (Two factor ANOVA with replication). However, the interactions of dietary protein deficiency and aluminum exposure were significant in cerebral and thalamic area. The aluminum-induced changes in SSA content in these two regions of adequately protein-fed animals (cerebrum : 59% and tha-
lamic area: 48%) were found to be significant (Scheffe’s F test for multiple comparisons). In addition, single factor ANOVA were also significant in these two regions of brain.

Discussion

It would appear from the Table 1 that, dietary protein restriction had no significant impact on regional aluminum level. Significant increases in aluminum contents of cerebrum, thalamic area and midbrain-hippocampal region of both the dietary groups have been observed in response to aluminum exposure. The midbrain-hippocampal region of the aluminum-exposed rat brain showed highest level of accumulation of aluminum. This observation is in agreement with the available reports indicating hippocampus to be the susceptible brain region for accumulation of aluminum [14–16]. However, the regional differences in increment of aluminum level on exposure to aluminum are comparable in both the dietary regimens. Like the earlier studies, insignificant impingement by protein restriction [10–12, 17] was observed also in the present study (Table 1).

Both aluminum and glutamate are inducers of paired helical filament formation [18] and have been implicated in neuronal damage and/or death in certain neurodegenerative disorders in humans [19]. Reports available on interaction between aluminum and glutamate are controversial. Glutamate is a potential binder of aluminum in physiological solutions [20]. Jones and Oorschot [21] had reported the absence of aluminum-induced conformational changes in tau protein when applied in combination with glutamate. However, aluminum is reported to cross the blood-brain barrier as glutamate [22] and can accelerate the aging process [23]. In vitro, aluminum is reported to potentiate glutamate-induced calcium accumulation in cerebellar granule cells [24] as well as enhance the glutamate-mediated cytotoxicity in hippocampal cell cultures [19].

Regional brain glutamate levels of rats maintained on adequate protein diet were found to be increased (significantly or insignificantly) in response to aluminum exposure (Table 2). This observation is in corroboration with earlier study of aluminum-induced rise in glutamate levels in different regions of brain [10]. This increment was not observed when the animals were maintained with low protein diet (Table 2). It appears from the present investigation that when the basal concentration of brain glutamate remained elevated, as in protein malnutrition, most of the regions of the brain except cerebellum responded to aluminum exposure differently in terms of glutamate level alteration i.e. decrease in contrast to elevation (Table 2). The responses of the cerebellum glutamate level to aluminum exposure in dietary protein adequacy and inadequacy were comparable. These varied responses of regional glutamate level, due to aluminum exposure, may modulate the region specific glutamate metabolism or vice versa as suggested by aluminum-induced alteration of glutamate transaminase [17] glutamate dehydrogenase [25] and glutamate decarboxylase [26] activities. On the other hand, it is also possible that the variation in the response of one or more of the enzymes linked to glutamate metabolism to aluminum exposure may also account for the observed alteration in the glutamate level in the affected regions of the brain in dietary protein adequacy or inadequacy.

In response to aluminum exposure to the adequately protein-fed rats, glutamate α-decarboxylase (GAD) activities of cerebrum and midbrain-hippocampal regions were found to be significantly increased whereas those of thalamic area and cerebellum were found to be insignificantly increased. Though, Hofstetter et al [26] observed an inhibition of GAD activity in rabbit brain, earlier study by us [10] support the present observation. The GAD activities of tested brain regions of protein restricted rats were found to be significantly or insignificantly reduced in response to aluminum exposure (Table 3). These observations of altered responses of glutamate level and GAD activity of brain of protein restricted animals suggested that the response of GAD may be dependent on the availability of its substrate glutamate.

Protein malnutrition was reported to produce an increase in brain γ-aminobutyric acid (GABA) level [27]. However, Colombo et al [9] did not find any increase in brain GABA level in protein malnutrition. Unlike regional glutamate level in the present investigation, GABA level does not vary significantly in response to aluminum exposure. In almost all brain regions, the GABA content remains unaltered with the exception of cerebellum of low-protein group in response to aluminum exposure (Table 3). These findings indicate that GABA levels of almost all brain regions can withstand aluminum insult either in dietary protein adequacy or inadequacy. However, in dietary protein restriction, the cerebellum becomes susceptible to aluminum-induced alteration.

The observed changes in the activity of GABA-synthesizing enzyme, GAD, were not always correlated with the regional GABA level, which suggested that GABA-degrading enzymes also play a role in maintaining the GABA level. The GAD activity showed significant increase in all the regions of brain in response to aluminum exposure. But the γ-aminobutyric acid transaminase (GABA-T; the major GABA degrading enzyme) activity was found to alter in a region specific and dietary protein specific manner (Table 4). Glutamate was reported to be increased in the brain of protein-restricted rats [9] and it is a specific binder to alu-
minum ion [20,28]. Hence, alterations in GAD and GABA-T activities observed in normal dietary protein group in response to aluminum exposure were reversed or tended to neutralized in protein-restricted group and glutamate may have played an important role in this. Both aluminum-induced glutamate accumulation and glutamate accumulation due to low-protein diet are toxic to brain cell. When the former may produce neuronal cell death through NH₃ accumulation [28], the latter can produce excitotoxic effect through NMDA receptor [29]. Thus, it may be suggested that when glutamate level reaches a critical level by the summated effects of aluminum exposure and protein malnutrition, the cellular defense mechanism(s) is (are) triggered which ultimately causes reversal or neutralization of the effects. On the other hand, the differential distribution of aluminum may have been implicated in the region specificity of alterations.

Besides glutamate decarboxylase and related aminotransferases [17], other enzymes, such as, glutamate dehydrogenase, γ-glutamyl transferase, glutamine synthase, glutaminase, etc. may be involved in the altered metabolism of glutamate leading to modulation of its level. For example, alteration in the activity of some of these enzymes in brain leads to modulation of brain glutamate level in protein deficiency or protein-energy deprivation [30–33]. Although the level of GABA in a specific region is regulated by the relative activity of GAD and GABA-T [34], transformations of GABA to other products (γ-aminobutyric acid, homocarnisine, homoanserine, γ-butyrobetaine, γ-amino-β-hydroxy butyric acid, γ-amino butyryl choline, etc.) in brain are also important [35]. Aluminum might cause alterations in these alternative pathways also and this in turn may lead to modulation of GABA levels which are not correlated with the relative activity of GAD and GABA-T.

Increased glutamate level was suggested to cause inhibition of GAD by promoting dissociation of pyridoxal phosphate (PLP) from the GAD apoenzyme, in spite of tight binding between PLP and GAD [35]. But, the results of the present investigation suggest that phenomenon occurring within the brain is not so simple, because there was an increase in GAD activity, which is not envisaged. Similarly, the alterations in SSA levels are not corroborating the changes in GABA-T activities. However, the mechanism of these varied effects of aluminum in brain glutamate and GABA systems is not clear and require further detailed study.

Conclusions

Thus the dietary protein status plays a significant role in the aluminum-induced alterations of the brain glutamate and GABA systems. The alterations of regional brain glutamate and γ-aminobutyrate levels by aluminum are region specific as well as dependent on dietary protein intake. The impact of aluminum exposure on the metabolism of these amino acid neurotransmitters are also influenced by dietary protein level. Thus, modification of dietary protein level or manipulation of the brain amino acid homeostasis by any other means may be a useful tool to find out a path to restrict amino acid neurotransmitter alterations in aluminum-associated neurodisorders. However, this requires further extensive study with different levels of modification in dietary protein.

Methods

Animals and diets

Male albino rats of Wistar strain weighing 100–120 g were divided into four groups of almost equal average body weight. The animals of two groups were maintained on the diet containing 18% protein (casein) while the remaining two groups were maintained on 6% protein (casein) diet as reported earlier [11]. One group of rats from each of the two dietary regimens received 4.2 mg /Kg body weight / day as aluminum chloride (AlCl₃.6H₂O) intra-peritoneally for four weeks and the animals of the remaining groups serving as pair-fed controls received only the physiological saline as reported elsewhere [12].

Tissue collection

After the period of treatment, the animals were kept fasting overnight, and then sacrificed by cervical dislocation. The whole brain was removed, washed with ice-cold saline, blotted dry and immediately transferred to the ice chamber. Cerebrum, thalamic area, midbrain-hippocampal region and cerebellum were separated as described elsewhere [11].

Biochemical estimations

Regional aluminum and protein contents were measured by atomic absorption spectroscopy of the acid digested samples and modified Folin Ciocalteau method, respectively as employed by Nayak and Chatterjee [11]. Regional glutamate, GABA and succinic semialdehyde contents and activities of glutamate-α-decarboxylase and GABA-transaminase were estimated following the methods as described by Nayak and Chatterjee [10]. Glutamate level of protein free homogenates were measured spectrophotometrically using sodium tartarate and ninhydrin whereas, in case of GABA measurement, the fluorophores development was carried out using copper tartarate and ninhydrin. Glutamate α-decarboxylase activities were assayed by measuring production of GABA spectrophotometrically. GABA transaminase activity was assayed by measuring succinic semialdehyde (SSA) production spectrophotometrically. The SSA levels were measured by spectrophotometric estimation of color complex produced by 3-methyl-2-benzothiazolone-2-hydrazone (MBTH) in the presence of ferric chloride and acetone.
Authors' contributions
PN carried out the literature survey, experimental works and statistical calculation. AKC conceived of the study, and participated in its design and coordination. All authors read and approved the final manuscript.

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