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Nano-alumina toxicity and computational covariance ratio of monoamines and amino acids at different brain area in male albino rats

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Abstract Nano-alumina toxicity refers to the potential harmful effects of nanoparticles of alumina on living organisms and easily penetrate all tissue and across blood brain barrier. The aim of the present study to conducted the correlation and physiological affected parameters under acute Al toxicity. The study started with twenty rats divided into two groups 10 rats for each: Control group (Con), Toxic group (Al-Nano) received single dose of intranasal (1.66g/kg Al2O3NPs) then all rats were scarified and brain dissected to four brain area (Hippocampus, Cortex, brain stem, and midbrain). Our results suggest that the Al2O3NPs stimulate the positive correlation between aspartic acid, glutamic acid, 5HIAA and negative correlation between aspartic acid, glutamic acid, 5HIAA vs. Glycin, NE, DA, 5HT, and GABA levels. In the same manner there were positive correlation between Glycine, NE, DA, and 5HT level for each brain area with different potent correlation level. This study concluded that Al2O3NPs exerted the negative cascade of monoamines concentration and secretion concurrent with the high level of aspartic, glutamic acid and serotonin metabolites (5HIAA).

Keywords Nano-alumina Correlation, Monoamines and amino acids, Brain, Rats.

1. Introduction

Although silicon and oxygen are the two chemical elements with the highest abundances in the Earth's crust, aluminum (Al) is regarded as the most prevalent metal there [1]. Al levels in the environment have significantly increased as a result of the intensive development of the Al industry and widespread use of the metal [2]. The diet, which accounts for 95% of the body's total amount of Al, drinking water, air, as well as cosmetics and medications, namely antacids, are possible sources of human Al exposure. Workplace exposure to aluminum can also come through involvement in the processing of aluminum [3]. Due to the availability of aluminum adjuvants, which are currently not commonly utilized and hence reduce the risk of vaccine-associated Al exposure, earlier studies have shown that vaccination could be considered as a source of aluminum exposure [4]. Al is a non-essential element that has been found to be hazardous to people, causing problems with their health such bone pathology and breast cancer [5]. Previous research showed a link between obesity, metabolic syndrome laboratory indicators, and markers of Al exposure. However, there is a dearth of information on the harmful effects of Al exposure [6]. Recent research has shown that Al poisoning may be directed towards the brain, leading to neurodegenerative and neurodevelopmental problems [7]. The link between brain Al buildup and neurological illnesses like Alzheimer's

disease, multiple sclerosis, and autism spectrum disorder has been underlined in recent thorough research by Exley and the coauthors [8]. By applying hyphenated approaches, speciation analysis has shown that Al exposure causes unique bioligand responses in exposed neural cells [9]. The third most prevalent and pervasive element in the planet is aluminum. It can be found in water, soil, and air in nature. Additionally, this substance can be unlawfully added to many foods and medications because it has been given the GRAS (generally recognized as safe) certification by the FDA (Food and Drug Association). Aluminum has the potential to pose a serious harm to people, animals, and plants, according to recent studies on environmental poisoning [10]. Oxidative stress is caused by aluminum overdose and affects the kidney, liver, and brain. It is possible to increase free radicals and alter the enzymes' ability to act as antioxidants [11]. Any contact with aluminum can alter the operation of a number of enzymes, alter how proteins are made, how nucleic acids work, and how permeable cell membranes. Additionally, it may have an impact on the body's metabolism of triglycerides and their plasma levels [12]. Due to its prooxidant properties, aluminum can cause biological oxidation both in vitro and in vivo. With decreased glutathione (GSH) levels, glutathione peroxidase (GSH-Px), glutathione S-transferase (GST), and catalase (CAT) activity in renal tissue, aluminum causes lipid peroxidation (LPO) [13]. Aluminum builds up in renal tissue, which causes renal-tubular cells to deteriorate, alters cellular metabolism, and stimulates oxidative stress, all of which result in sodium and water imbalances, altered p-aminohippuric acid transport, and ultimately, renal toxicity [14]. The primary protein complex in the P-type ATPase family found in all living things is sodium-potassium ATPase. It contributes to the preservation of the cell's homeostasis and gradient both inside and outside the cell. Na+/K+ ATPase is inhibited by aluminum both in vitro and in vivo [15]. Reactive oxygen species (ROS) produced by aluminum cause lipid peroxidation and DNA and protein oxidative damage. Iron that is bound to transferrin and iron that isn't coupled to transferrin are both removed more quickly from human brain cells when aluminum levels are low. The quantity of iron bound to ferritin also decreases. Increased oxidative stress may be indicated by an increase in the cytoplasmic pool of iron. However, the defensive enzymes of the cell, such as catalase, glutathione reductase, superoxide dismutase, and glutathione reductase, were unaffected by the elevated iron concentration. While the activity of catalase, glutathione peroxidase, and superoxide dismutase reduced when aluminum was administered orally, lipid peroxidation levels noticeably rose [16]. According to studies, even trace levels of aluminum in the brain may affect the iron homeostasis there, leading to neurodegenerative diseases [17]. Corticoneuronal apoptosis can be brought on by aluminum, and it's conceivable that the SAPK/JNK signal transduction pathway—also known as c-jun N-terminal kinase or stress-activated protein kinase—plays a significant role in this instance. The transcription factor NF-kB is also involved in many regulatory pathways and is controlled by a variety of signaling events. Numerous genes, proinflammatory cytokines, immunological receptors, cell adhesion molecules, chemokines, and microRNAs are all regulated by the NF-kB family [18].

The aim of present study aimed to investigate the correlation between neurotransmitters and brain amino acids under acute Al toxicity.

2. Materials and Methods

2.1 Animals and Experimental Procedures

Healthy adult male albino rats, Rattus norvegicus, with an average body weight 200 ± 10 g, were used as an experimental model for the present work. Rats were purchased from the animal facility of VACSERA, Cairo, Arab Republic of Egypt. Animals were acclimatized to laboratory conditions for two weeks prior to the experiments, and then housed in polyethylene cages in the air-conditioned animal house at an average temperature of 23±1°C, relative humidity of 20%, and cyclic daylight for 12 hours/day. The animals had access ad libitum to water and a balanced commercial pelleted diet that was obtained from the feed plant of the Atmida Poultry Company, Dakahilia Governorate, Egypt. The food debris and feces were removed from cages and were cleaned daily to keep sawdust dry throughout the course of experiments. The present experimental procedures were conducted in accordance with the international guideline principles for the care and use of laboratory animals in scientific research (NRC, 2011). All the experiments were done under normal laboratory environmental conditions at the Zoology Department, Faculty of Science, Helwan University, Cairo, Egypt.

A total number of 20 male albino rats will be allocated into 2 groups 10 per group according to the following scheme: Group I: Animals in this group will be intranasal administrated normal saline (0.1 ml/rat) for one day served as normal control. Group 2: Animals in this group will be intranasal administrated nanoalomina (1.66g/kgAl_2O_3NPs) for one day served as positive control after24h of dosage.

Determination of the free amino acid content in the brain tissue by HPLC:

Sample preparation:

The first step for determination of amino acids by HPLC method involved weighing and homogenization of the tissue in 1/10 weight/volume of 75% methanol HPLC grade. The homogenate was spun at 4000 r.p.m. for 10 min and the supernatant dried using vacuum (70 millipore) at room temperature.

Derivatization procedure:

The derivatization started by re-drying the sample under test using drying solution consisted of 2:2:1 mixture (by volume) of methanol: 1M sodium acetate trihydrate: triethylamine (TEA). The drying solution was added to the dry sample, shook well and then put under vacuum till complete dryness. The derivatizing agent consisted of 7:1:1:1 mixture (by volume) of methanol: TEA: double distilled deionized water: PITC. The derivatizing solution was added to the re-dried sample, shook well and left to stand at room temperature for 20 min, then applied to vacuum (70 millitore) till dryness. The dry sample was then diluted by a sample diluent composed of 0.71-g disodium-hydrogen phosphate adjusted to a pH of 7.4 by the use of 10% phosphoric acid. Acetonitrile was then mixed, as 5% by volume with the resulting solution. Derivatized amino acids standards and derivatized samples were injected, into the column for separation by HPLC.

Chromatographic conditions:

Free amino acid neurotransmitters were detected by high performance liquid chromatography (HPLC) using the precolumn phenylisothiocyanate (PITC) derivatization technique according to the method of Heinrikson and Meredith (1984). The HPLC system of Agilent consisted of quaternary pump; a column oven, Rheodine injector and 20µl loop, UV variable wavelength detector. The report and chromatogram taken from chemstation program. PICO-TAG column (Waters) for free-amino acid analysis 3.9 x 30 cm. Eluent (1) and Eluent (2), Phenylisothiocyanate (PITC), Triethylamine, Amino acids standard. (Standards and Eluents are Waters chemistry package for free amino acids). The assay conditions were as follows: temperature: 46 °C; wave-length: 254 nm; flow rate: 1ml/min [19].

Determination of the brain monoamine concentrations by HPLC

Sample preparation:

The determination of monoamines and its metabolites by HPLC method involved weighing and homogenization of the tissue in 1/10 weight/volume of 75% methanol HPLC grade. The homogenate was spun at 4000 r.p.m. for 10 min and the supernatant were used after filtration with nylon filter (0.45µm) immediate or stored at -20◦C till assay. The assay was carried out for monoamines according to the method described by Pagel, et al. (2000).

Chromatographic conditions:

The HPLC system of Agilent 1260 technologies. The sample was then injected directly into an Aqua® 5 µm C18 125 Å, LC Column 250 x 4.6 mm, Ea, purchased from Phenomenex, USA under the following conditions: mobile phase 97/3, 20 mmole potassium phosphate, pH 3.0/ methanol, flow rate 1.5ml/min, UV 270 nm. [20].

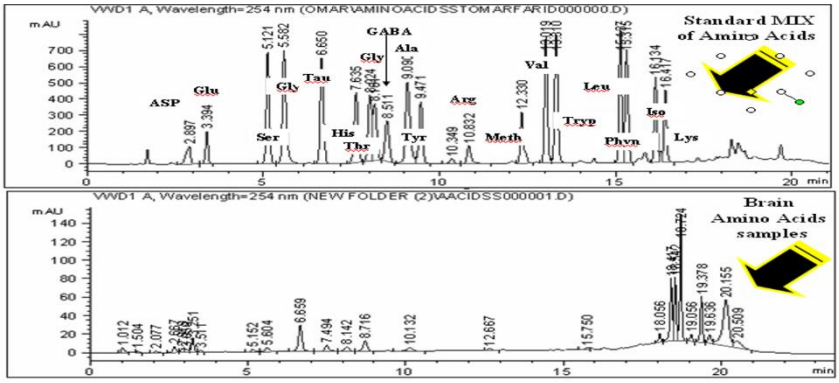

Figure 1: Determination of the free amino acid content in the brain tissue by HPLC

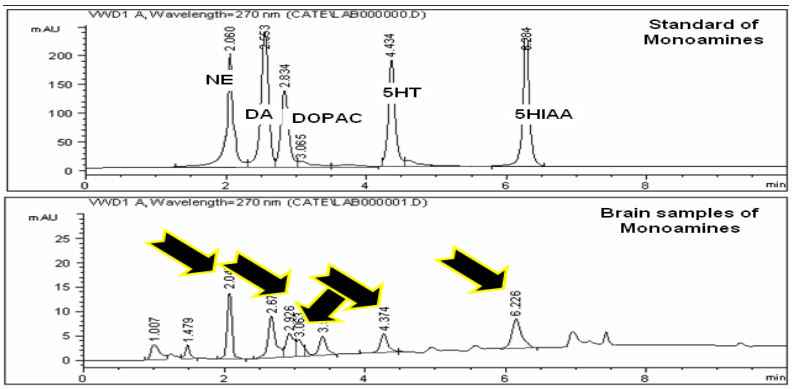

Figure 2: Determination of the monoamines content in the brain tissue by HPLC

Statistical analysis:

Statistical analysis of the obtained data was performed Statistical Analysis Systems Institute (SAS, 2004). Significant correlation among individuals were evaluated using Pearson product-moment correlation coefficient (PPMCC).

3. Results

Table 1: Colored person correlation matrix for neurotransmitters, excitatory and inhibitory amino acids in hippocampus brain area

1.0 -1.0

	HippGly	HippNE	Hipp5HT	HippDA	HippGABA	HippASP	Hipp5HIAA	HippGLU
HippGly	1	0.417 P=0.0672 n=20	0.484 P=0.0306 n=20	0.587 P=0.0066 n=20	0.575 P=0.0080 n=20	-0.478 P=0.0330 n=20	-0.616 P=0.0038 n=20	-0.535 P=0.0152 n=20
HippNE	0.417 P=0.0672 n=20	1	0.295 P=0.2063 n=20	0.531 P=0.0159 n=20	0.298 P=0.2013 n=20	-0.317 P=0.1734 n=20	-0.321 P=0.1679 n=20	-0.548 P=0.0125 n=20
Hipp5HT	0.484 P=0.0306 n=20	0.295 P=0.2063 n=20	1	0.359 P=0.1198 n=20	0.584 P=0.0069 n=20	-0.561 P=0.0101 n=20	-0.620 P=0.0035 n=20	-0.459 P=0.0419 n=20
HippDA	0.587 P=0.0066 n=20	0.531 P=0.0159 n=20	0.359 P=0.1198 n=20	1	0.389 P=0.0901 n=20	-0.577 P=0.0078 n=20	-0.547 P=0.0125 n=20	-0.658 P=0.0016 n=20
HippGABA	0.575 P=0.0080 n=20	0.298 P=0.2013 n=20	0.584 P=0.0069 n=20	0.389 P=0.0901 n=20	1	-0.693 P=0.0007 n=20	-0.569 P=0.0088 n=20	-0.640 P=0.0024 n=20
HippASP	-0.478 P=0.0330 n=20	-0.317 P=0.1734 n=20	-0.561 P=0.0101 n=20	-0.577 P=0.0078 n=20	-0.693 P=0.0007 n=20	1	0.742 P=0.0002 n=20	0.719 P=0.0004 n=20
Hipp5HIAA	-0.616 P=0.0038 n=20	-0.321 P=0.1679 n=20	-0.620 P=0.0035 n=20	-0.547 P=0.0125 n=20	-0.569 P=0.0088 n=20	0.742 P=0.0002 n=20	1	0.577 P=0.0078 n=20
HippGLU	-0.535 P=0.0152 n=20	-0.548 P=0.0125 n=20	-0.459 P=0.0419 n=20	-0.658 P=0.0016 n=20	-0.640 P=0.0024 n=20	0.719 P=0.0004 n=20	0.577 P=0.0078 n=20	1

Obtained data of table 1. Showed that there is moderate negative correlation between Gly, NE, DA, GABA against glutamic, Asp, and 5HIAA. In addition, there were weak negative correlation against with the 5HT, against excitatory amino acids and 5HIAA. In contrast the tighter parameters with positive correlation resembling at the levels of monoamines with the same behavior and inhibitory amino acids (GABA, and Gly) these parameters were not roundly to red color which proof the moderate correlation.

Table 2: Colored person correlation matrix for neurotransmitters, excitatory and inhibitory amino acids in cortex brain area

1.0 -1.0

	Cortex5HT	CortexGABA	CortexDA	CortexGly	CortexNE	Cortex5HIAA	CortexGLU	CortexASP
Cortex5HT	1	0.848 P<0.0001 n=20	0.744 P=0.0002 n=20	0.723 P=0.0003 n=20	0.610 P=0.0043 n=20	-0.664 P=0.0014 n=20	-0.776 P=0.0001 n=20	-0.802 P<0.0001 n=20
CortexGABA	0.848 P<0.0001 n=20	1	0.559 P=0.0103 n=20	0.680 P=0.0010 n=20	0.596 P=0.0056 n=20	-0.661 P=0.0015 n=20	-0.677 P=0.0010 n=20	-0.780 P=0.0001 n=20
CortexDA	0.744 P=0.0002 n=20	0.559 P=0.0103 n=20	1	0.739 P=0.0002 n=20	0.765 P=0.0001 n=20	-0.643 P=0.0022 n=20	-0.815 P<0.0001 n=20	-0.762 P=0.0001 n=20
CortexGly	0.723 P=0.0003 n=20	0.680 P=0.0010 n=20	0.739 P=0.0002 n=20	1	0.711 P=0.0004 n=20	-0.759 P=0.0001 n=20	-0.841 P<0.0001 n=20	-0.857 P<0.0001 n=20
CortexNE	0.610 P=0.0043 n=20	0.596 P=0.0056 n=20	0.765 P=0.0001 n=20	0.711 P=0.0004 n=20	1	-0.777 P=0.0001 n=20	-0.861 P<0.0001 n=20	-0.763 P=0.0001 n=20
Cortex5HIAA	-0.664 P=0.0014 n=20	-0.661 P=0.0015 n=20	-0.643 P=0.0022 n=20	-0.759 P=0.0001 n=20	-0.777 P=0.0001 n=20	1	0.800 P<0.0001 n=20	0.734 P=0.0002 n=20
CortexGLU	-0.776 P=0.0001 n=20	-0.677 P=0.0010 n=20	-0.815 P<0.0001 n=20	-0.841 P<0.0001 n=20	-0.861 P<0.0001 n=20	0.800 P<0.0001 n=20	1	0.828 P<0.0001 n=20
CortexASP	-0.802 P<0.0001 n=20	-0.780 P=0.0001 n=20	-0.762 P=0.0001 n=20	-0.857 P<0.0001 n=20	-0.763 P=0.0001 n=20	0.734 P=0.0002 n=20	0.828 P<0.0001 n=20	1

Obtained data of Table 2. Showed that the cortex is a major brain area affected by poisoning and all parameters tightly correlated after exposure with blue color at the negative direction or firm orange roundly to red for positive direction. The data are in agreement with the basis of science which illustrate negative correlation between inhibitory and excitatory amino acids.

Table 3: Colored person correlation matrix for neurotransmitters, excitatory and inhibitory amino acids in brain stem.

1.0 -1.0

	BSDA	BSGly	BSGABA	BSNE	BS5HT	BS5HIAA	BSASP	BSGLU
BSDA	1	0.553 P=0.0114 n=20	0.438 P=0.0533 n=20	0.210 P=0.3748 n=20	0.322 P=0.1660 n=20	-0.282 P=0.2275 n=20	-0.124 P=0.6028 n=20	-0.634 P=0.0027 n=20
BSGly	0.553 P=0.0114 n=20	1	0.429 P=0.0589 n=20	0.041 P=0.8647 n=20	0.313 P=0.1787 n=20	-0.216 P=0.3597 n=20	-0.213 P=0.3677 n=20	-0.639 P=0.0024 n=20
BSGABA	0.438 P=0.0533 n=20	0.429 P=0.0589 n=20	1	0.300 P=0.1987 n=20	0.576 P=0.0078 n=20	-0.501 P=0.0246 n=20	-0.365 P=0.1131 n=20	-0.652 P=0.0018 n=20
BSNE	0.210 P=0.3748 n=20	0.041 P=0.8647 n=20	0.300 P=0.1987 n=20	1	0.530 P=0.0163 n=20	-0.358 P=0.1209 n=20	-0.547 P=0.0126 n=20	-0.329 P=0.1569 n=20
BS5HT	0.322 P=0.1660 n=20	0.313 P=0.1787 n=20	0.576 P=0.0078 n=20	0.530 P=0.0163 n=20	1	-0.490 P=0.0284 n=20	-0.698 P=0.0006 n=20	-0.490 P=0.0283 n=20
BS5HIAA	-0.282 P=0.2275 n=20	-0.216 P=0.3597 n=20	-0.501 P=0.0246 n=20	-0.358 P=0.1209 n=20	-0.490 P=0.0284 n=20	1	0.276 P=0.2383 n=20	0.387 P=0.0916 n=20
BSASP	-0.124 P=0.6028 n=20	-0.213 P=0.3677 n=20	-0.365 P=0.1131 n=20	-0.547 P=0.0126 n=20	-0.698 P=0.0006 n=20	0.276 P=0.2383 n=20	1	0.264 P=0.2606 n=20
BSGLU	-0.634 P=0.0027 n=20	-0.639 P=0.0024 n=20	-0.652 P=0.0018 n=20	-0.329 P=0.1569 n=20	-0.490 P=0.0283 n=20	0.387 P=0.0916 n=20	0.264 P=0.2606 n=20	1

Obtained data of Table 3. Showed that there is moderate negative correlation between DA, Gly, GABA against glutamic. In addition, there were weak negative correlation against NE and 5HT, against Asp and 5HIAA. In contrast the mild tight correlation at the positive direction for monoamines and inhibitory amino acids and with self-concentrations.

Table 4: Colored person correlation matrix for neurotransmitters, excitatory and inhibitory amino acids in midbrain

1.0 -1.0

	MBGLU	MBGABA	MBNE	MBASP	MB5HT	MBGly	MB5HIAA	MBDA
MBGLU	1	0.511 P=0.0212 n=20	-0.034 P=0.8875 n=20	-0.160 P=0.5002 n=20	-0.132 P=0.5784 n=20	0.395 P=0.0847 n=20	0.168 P=0.4779 n=20	-0.414 P=0.0693 n=20
MBGABA	0.511 P=0.0212 n=20	1	-0.288 P=0.2177 n=20	-0.060 P=0.8027 n=20	-0.038 P=0.8740 n=20	0.084 P=0.7254 n=20	0.214 P=0.3653 n=20	-0.198 P=0.4036 n=20
MBNE	-0.034 P=0.8875 n=20	-0.288 P=0.2177 n=20	1	0.104 P=0.6640 n=20	0.064 P=0.7891 n=20	0.453 P=0.0449 n=20	0.001 P=0.9954 n=20	-0.137 P=0.5639 n=20
MBASP	-0.160 P=0.5002 n=20	-0.060 P=0.8027 n=20	0.104 P=0.6640 n=20	1	0.125 P=0.5985 n=20	-0.187 P=0.4289 n=20	-0.066 P=0.7813 n=20	0.323 P=0.1646 n=20
MB5HT	-0.132 P=0.5784 n=20	-0.038 P=0.8740 n=20	0.064 P=0.7891 n=20	0.125 P=0.5985 n=20	1	0.241 P=0.3067 n=20	-0.312 P=0.1799 n=20	0.237 P=0.3134 n=20
MBGly	0.395 P=0.0847 n=20	0.084 P=0.7254 n=20	0.453 P=0.0449 n=20	-0.187 P=0.4289 n=20	0.241 P=0.3067 n=20	1	-0.296 P=0.2057 n=20	-0.556 P=0.0109 n=20
MB5HIAA	0.168 P=0.4779 n=20	0.214 P=0.3653 n=20	0.001 P=0.9954 n=20	-0.066 P=0.7813 n=20	-0.312 P=0.1799 n=20	-0.296 P=0.2057 n=20	1	0.183 P=0.4399 n=20
MBDA	-0.414 P=0.0693 n=20	-0.198 P=0.4036 n=20	-0.137 P=0.5639 n=20	0.323 P=0.1646 n=20	0.237 P=0.3134 n=20	-0.556 P=0.0109 n=20	0.183 P=0.4399 n=20	1

Obtained data of table 4. Showed that there is mild or weak correlation with variated distribution of midbrain are which rounded for green color. In contrast there were moderate negative correlation of Gly vs. DA for midbrain. In the same manner yellow color means moderate correlation at the positive direction which view at GABA vs Glu and Gly vs. Glu, and NE.

4. Discussion

Alumina, or aluminum oxide, is a compound made up of aluminum and oxygen [21]. It is widely used in various industries, including the production of aluminum, ceramics, and electronics [22]. Alumina nanoparticles can cause toxicity in various organs and systems, including the immune system. Inhalation of alumina nanoparticles can lead to inflammation in the lung parenchyma and trigger aluminosis [23]. The toxicity of nano-alumina is influenced by factors such as particle size and chemical composition. Nano-sized alumina particles were found to be more toxic than micro-sized particles [24].

Alumina is widely present in the diet, with higher levels found in vegetable, fruit, and seafood groups. It is added to drinking water as a flocculant, used as an additive in processed foods, and can be present in fresh foods due to the aluminum content in soils [25]. Alumina can be a source of exposure through various means. industries such as aluminum smelting, welding, mining, and processing of ore and scrap metal recycling can be exposed to alumina nanoparticles [26]. Environmental media such as soil, water, and air can be contaminated by alumina from anthropogenic sources and weathering of rocks and minerals. Alumina is widely present in the diet, with higher levels found in vegetable, fruit, and seafood groups. It is added to drinking water as a flocculant, used as an additive in processed foods, and can be present in fresh foods due to the aluminum content in soils. Alumina can also be absorbed through the skin from cosmetics, especially antiperspirants [27].

The mechanism of alumina toxicity involves several processes and effects on cells and tissues. Here is a summary of the information from the search results. Inhibition of enzyme activity and protein synthesis: Aluminum toxicity, including that of alumina nanoparticles, can lead to the inhibition of enzyme activity and protein synthesis. This disruption in cellular processes can have detrimental effects on various organ systems [28].

The dopamine and norepinephrine pathway are an important system in the brain that regulates various functions, including arousal, attention, cognitive function, stress reactions, and reward processes. Dopamine and norepinephrine are both catecholamines synthesized from the precursor amino acid tyrosine through a series of enzymatic reactions [29]. The rate-limiting step in this synthesis pathway is the activity of the enzyme tyrosine hydroxylase. In addition, dopamine is actively transported from the cytoplasm into vesicles by the vesicular monoamine transporter. Norepinephrine, on the other hand, is synthesized within the vesicles from dopamine by the enzyme dopamine beta-hydroxylase. Both dopamine and norepinephrine bind to adrenergic receptors, including α1, α2, and β receptors [30]. The binding of norepinephrine to its receptor activates second messenger signaling

pathways, which play a role in modulating synaptic function [31]. Finally, dopamine signaling is terminated by reuptake into the presynaptic terminal via the dopamine transporter (DAT). Once inside the cell, dopamine is either degraded by monoamine oxidase (MAO) or catechol-O-methyltransferase (COMT), or it is repackaged into vesicles. Norepinephrine can be degraded intracellularly or in the synaptic cleft by MAO and COMT. These pathway in agreement with pathway of positive correlation between NE and DA specially at cortex brain area [32]. serotonin is an important neurotransmitter that play a role in regulating various bodily functions, including emotions, movement, coordination, pleasure, reward, digestion, metabolism, and cognition [33]. serotonin acts through several 5-HT receptors in the brain to modulate dopamine neurons in all three major dopaminergic pathways. Both neurotransmitters relay messages between neurons and affect mood and concentration, but they have some distinct functions [34].

Monoamines, have various responses to alumina toxicity. neuronal cell has been found that glutamate toxicity via the oxidative pathway requires monoamine metabolism as a source of free radicals [35].

Alumina toxicity disrupt the monoamine oxidase inhibitor (MAOIs) that inhibit the enzyme monoamine oxidase, which is responsible for the deactivation of monoamines. When the inhibitory effects of MAOIs are amplified, there can be an increase in active monoamines, leading to manifestations of MAOI toxicity. Symptoms of MAOI toxicity may include hyperadrenergic crisis, tachycardia, hyperthermia, myoclonus, hypertension, and agitation [36].

The interaction between alumina and the glutamate and aspartate pathway in the brain may induce a toxic effect. The Inhibitory effect on glutamate binding on brain synaptic membranes [37]. This disruption in glutamate binding can affect synaptic function and neurotransmission. These interruptions induce frailer of neuromodulating cascades, including the glutamate/GABA-glutamine shuttle. In addition, the toxicity triggers the inflammation which lead to chronic neuroinflammation. This inflammation can affect the function of neurotransmitters, including glutamate and aspartate, and contribute to neurotoxicity [38]. Oxidative stress: Heavy metals can generate free radicals, leading to oxidative stress in the brain. This oxidative stress can damage lipids, proteins, and DNA molecules, contributing to neurotoxicity [39].

The alumina toxicity led to oxidative stress accumulation. The oxidative stress can affect the level of glutamate in the brain. the brain glutamic acid may be utilized by 40% of the synapses [40]. Glutamate is responsible for most of the excitatory synaptic activity and oxidative stress induction in the mammalian brain. Oxidative stress has been implicated in the pathogenesis of various neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's disease [41].

Acute stress can have detrimental effects on the brain, including increased glutamate release, impaired long-term potentiation (LTP), atrophy of the apical dendrites. Glutamate is a master neurotransmitter in the brain and is responsible for most of the excitatory synaptic activity and oxidative stress induction in the mammalian brain [42]. The second pathway for stress and glutamate, the imbalance of neural circuitry subserving cognition, anxiety, and mood that can increase or decrease expression of those behaviors and behavioral states. Stress can disrupt synapse regulation, resulting in the loss of sociability and the avoidance of interactions with others [43]. Stress can also cause an imbalance in the hypothalamic-pituitary-adrenal (HPA) axis, leading to the overproduction of cortisol. Cortisol as a stress marker can increase glutamate levels in the brain [44]. Many studies investigating the relationship between depression and oxidative stress, it was found that brain glutamate-mediated excitability was increased in depressed patients. acute stress rapidly releases cortisol, which enters the brain and produces rapid and slow onset effects, including effects on glutamate [45; 46]. Several studies investigating the relationship between oxidative stress and amino acids level, it was found that brain glutamate-mediated excitability was increased in stress. Acute stress effects on GABA and glutamate levels in the cortex have also been studied, and cortisol levels over time were significantly higher in the stress condition compared to the control condition. Both GABAergic and glutamatergic brain circuits modulate hypothalamus-pituitary-adrenal (HPA)-axis activity, and stress in turn affects glutamate and GABA [47; 48].

Many studies have indicated that GABA levels in the cortex are negatively correlated with anxious behaviors which in agreement with present study. This suggests that higher levels of Glu may be associated with reduced toxicity [49]. Another stress model such as ischemia, Ischemia-evoked release of glutamate, aspartate, and GABA was

compared in control vs. drug-treated animals. The results showed that increases in GABA levels were depressed by certain drug treatments, indicating a potential negative correlation between GABA and aspartate release in ischemic conditions [50].

Finally, obtained data suggested the three were negative correlation for monoamines and excitatory amino acids which inagreement with several studies reported the negative correlation for dopamine and aspartate in certain brain cortex. A study of schizophrenia found a negative correlation between plasma levels of dopamine metabolites and mismatch negativity (MMN) amplitude in patients with schizophrenia [51]. This suggests that higher levels of dopamine metabolites may be associated with reduced MMN amplitude. Another study in frontal cortex found a negative relationship between glutamate concentrations in the lateral prefrontal cortex and ventral striatum dopamine synthesis capacity. This suggests that higher glutamate levels may be associated with lower VS dopamine synthesis capacity [52].

5. Conclusion

Nano-alumina toxicity can cause damage to living organisms' brains due to its ability to penetrate all tissues and cross blood-brain barrier. A study investigated the correlation between aluminum oxide nanoparticle exposure and physiological parameters such as monoamine was declined. The exposed group showed a positive correlation between aspartic acid, glutamic acid, and 5HIAA while having negative correlations with Glycine, NE, DA, and GABA. This suggests that AlO3NPs stimulate an imbalance of neurotransmitter metabolism leading to potential harmful effects.

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