Chapter 3
Entry and Deposit of Aluminum in the Brain

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Abstract Aluminum, as a known neurotoxicant, contributes to cognitive dysfunction and may contribute to Alzheimer's disease. The important reason is that aluminum can enter and be deposited in the brain. There have been three routes by which aluminum could enter the brain from systemic circulation or the site of absorption. Aluminum fluxes into brain across the blood-brain barrier (BBB), the choroid plexuses and the nasal cavity. Some factors, such as the increasing of the blood-brain barrier permeability, citric acid and parathyroid hormone (PTH), and vitamin D, can promote aluminum to enter the brain. But the redistribution of aluminum out of the brain is slow, so aluminum can be deposited in the brain for a long time.

Keywords Aluminum · Entry · Deposit · Brain

Aluminum, as a known neurotoxicant, enters and is deposited in the brain, where it contributes to cognitive dysfunction and may contribute to Alzheimer's disease. High concentration of aluminum has been found in senile plaques and neurofibrillary tangles, which occur in the brains of subjects with Alzheimer's disease. There are certain evidences from clinical and experimental studies that oral, subcutaneous, abdominal cavity and respiratory aluminum exposure can increase brain aluminum. Human brain aluminum increased with exposure age, and animal brain aluminum increased with duration of aluminum exposure.

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Q. Niu (ed.), *Neurotoxicity of Aluminum*, Advances in Experimental Medicine and Biology 1091, https://doi.org/10.1007/978-981-13-1370-7_3

3.1 Aluminum Enters into the Brain

3.1.1 Aluminum Enters into the Brain Across BBB

Aluminum entering into the brain across the blood-brain barrier has been defined to be the primary route of brain aluminum uptake. The anatomical basis of the BBB is primarily attributed to the tight junctions between the cerebral microvascular endothelial cells that line the microvessels that perfuse the brain. Additional impediments to permeation through the BBB come from the absence of fenestrations and the low transcytotic activity of the endothelial cells, the pericytes that surround 30% of their surface, and the astrocyte foot processes that cover 99% of the surface of the endothelial and pericyte cells. Substances must either diffuse through the membranes of these cells or be transported by cell membrane carriers to penetrate the BBB. The surface area of the 400 miles of brain capillaries that are the site of the BBB is roughly 12 m^2. There is much greater opportunity for rapid exchange between the blood and brain through the BBB [1]. The potential mechanisms of distribution of substances across the BBB are the same as those across any cell membrane: diffusion, carrier-mediated and receptor-mediated transport by facilitated diffusion, and active transport. And aluminum could enter into the brain through all these ways.

3.1.1.1 Aluminum Influxes into the Brain Across BBB Directly as a Small Molecular Weight Pieces

It is generally believed that the BBB is restrictive for small molecules at capillary endothelial cells and for large molecules at the interendothelial tight junctions. It has been defined that some substances can influx into the brain penetratingly through BBB. The brain capillary permeability coefficient (P) is affected by molecular weight and the octanol/water partition coefficients. The relationship of permeability to octanol/water partition coefficient and molecular weight was found to be predictable for drugs with molecular weights less than 400. The roles of lipophilicity (hydrogen-bonding potential, polar surface area) and molecular weight as predictors for diffusion of small molecules across the BBB have been well described, providing the opportunity to estimate the permeability rates of aluminum and its complexes across the BBB from their octanol/buffer partitioning coefficient and molecular weight [2].

3.1.1.2 Aluminum Entry into the Brain Is Mediated by Transferrin (Tf)-Transferrin Receptor (TfR), Which Is an Important Iron Carrier Receptor

The prominent rate and extent mechanism by which aluminum transports across the blood-brain barrier are mediated by carrier receptor. The system of Tf-TfR is one of the important carrier receptors by which aluminum transports across BBB.

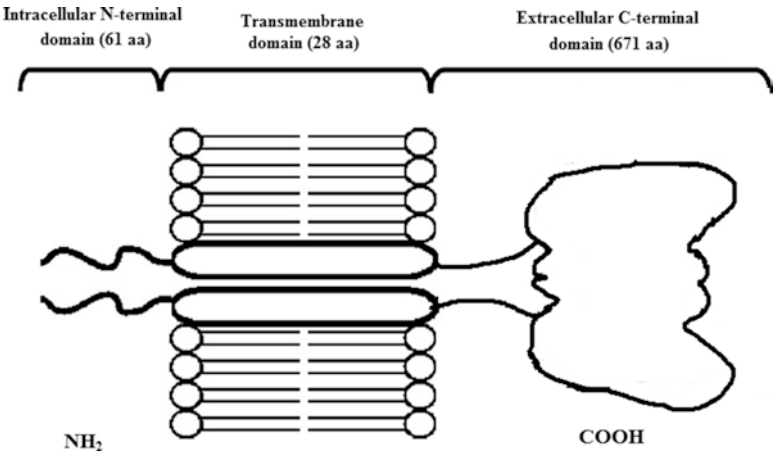

Fig. 3.1 TfR1

It is a possible route of entry for aluminum into the cells of the central nervous system via the same high-affinity receptor-ligand system that has been postulated for iron delivery to neurons and glial cells. It is defined that aluminum can enter into the brain under normal physiological conditions.

Tf is part of a family of proteins that includes serum Tf, ovotransferrin, and lactoferrin, which binds circulating Fe^{3+} and prevents it from traveling throughout the body in its toxic form. The Tf consists of a polypeptide chain of 679 amino acids in humans, and its monomer (80 kDa) is a glycoprotein that consists of two subunits (40 kDa each) known as the N-lobe and the C-lobe separated by a short spacer sequence. There is an iron binding site in between each N- and C-terminal sequences' globular lobe. Two tyrosines, one histidine, and one aspartic acid bind the iron ion to the transferrin in both lobes. Therefore each Tf molecule (apo-Tf) can transport one (monoferric Tf) or two (diferric Tf) iron atoms. The association constant for dimeric Tf and the TfR is 30-fold higher than that of monoferric Tf and 500-fold higher than apo-Tf. Diferric Tf represents approximately 10–30% of circulating Tf, leaving Tf to bind with other metal ions. Synthesis of Tf occurs primarily in hepatocytes, but small amounts are also synthesized in Sertoli, ependymal, and oligodendroglial cells. Tf transports and delivers iron into cells via interactions with its receptor [3].

The TfR (CD71) is a type II transmembrane glycoprotein that is found primarily as a homodimer (180 kDa) consisting of identical monomers joined by two disulfide bonds. Each monomer has 760 amino acids; its molecular weight is 90–95 kDa. It comprises a large extracellular C-terminal domain (671 amino acids) with an O-linked glycosylation site at threonine 104 and 3 N-linked glycosylation sites on arginine residues 251, 317, and 727 known as the ectodomain that includes the site of Tf-binding, a single-pass transmembrane domain with 28 amino acids and a short intracellular N-terminal domain with 61 amino acids (Fig. 3.1). The ectodomain includes a O-linked glycosylation site and three N-linked glycosylation sites. Glycosylation at these sites is required for adequate function of the receptor. It has

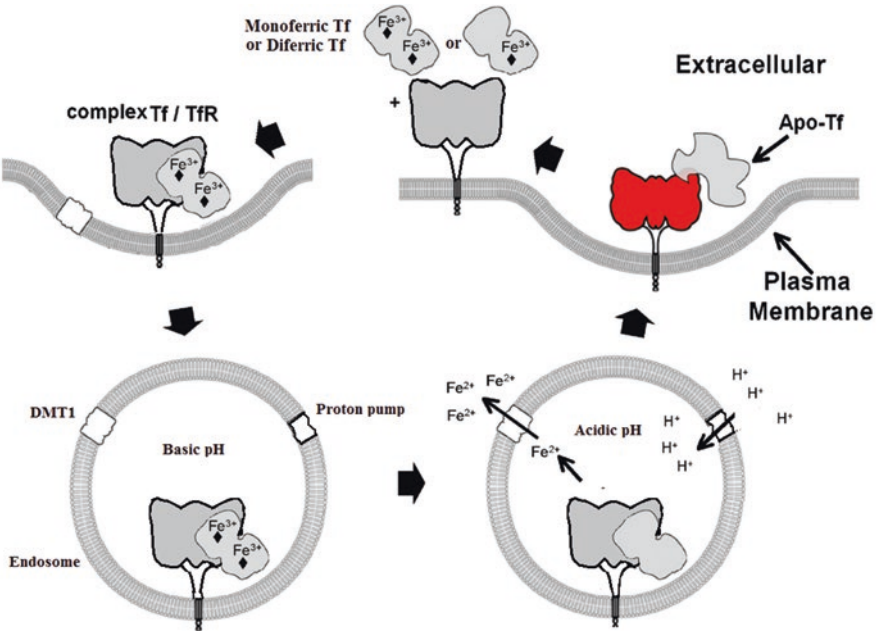

Fig. 3.2 Cellular uptake of iron through the Tf-TfR system

been previously demonstrated that the TfR phosphorylation on serine 24 in the intracellular domain is not required for internalization or recycling of the receptor. It is only an essential protein involved in iron uptake and the regulation of cell growth. Delivery and uptake of iron from Tf into cells occurred by the internalization of iron-loaded Tf are mediated by the TfR [3].

TfR is widespread in the central nervous system. The expression of TfR has also been observed on nonproliferating cells, including those of the vascular endothelium of brain capillaries. It exists in the hippocampus, pontine nucleus, reticular formation, arcuate nucleus, red nucleus, substantia nigra, several cranial nuclei, deep cerebellar nuclei, and cerebellar cortex, as well as in the cerebral cortex and brainstem neurons, choroid plexus cells, and brain capillary endothelial cells.

Cellular uptake of iron takes place through the Tf system via receptor-mediated endocytosis. There are two steps in the course of Fe^{2+} transporting into the nervous system: the first step is that a complex forms TfR on the endothelial cells combining to the Tf-Fe^{3+} and the second step is the release of iron. Endocytosis of the diferric or monoferric Tf/TfR complex occurs via clathrin-coated pits, and the complex is delivered into endosomes. Protons are pumped into the endosome resulting in a decrease in pH that stimulates a conformational change in Tf and its subsequent release of iron. The iron is then transported out of the endosome into the cytosol by the divalent metal transporter 1 (DMT1). Apo-transferrin remains bound to the TfR while in the endosome and is only released once the complex reaches the cell surface [3] (Fig. 3.2).

An ion like aluminum is easily bound to many substances and structures in the organisms. The ligands are often nonspecific and can bind other metal ions. Once aluminum enters the circulation, it is associated with several endogenous ligands. The major aluminum binding fraction of plasma has been shown to be transferrin (Tf), the chief iron transport protein in vertebrates. Tf specifically binds Al^{3+} with a high affinity, approaching its affinity for iron (Fe^{3+}); Tf-Fe^{3+} normally enters tissues throughout the body by receptor-mediated endocytosis of the TfR-$(Tf)_2$ complex. About 81% of aluminum in circulation was coffiplexed with transferrin.

It is identified that the system of Tf-TfR might mediate aluminum citrate transport across the BBB, a possible route of entry for aluminum to neurons and glial cells of the central nervous system via the same high-affinity receptor-ligand system that has been postulated for iron delivery. And aluminum is able to gain access to the central nervous system in normal physiological conditions [4].

Al^{3+} has been demonstrated to complex to specific binding sites on human Tf at physiological pH, and this association is ligand concentration dependent and reversible Al^{3+}; it's capable of gaining access to the cells in the central nervous system via this Tf-TfR interaction under normal physiological conditions. Some Tf complex could disrupt normal iron regulatory processes by binding in a relatively nondisplaceable manner with the TfR; the first part was the same high affinity of Tf-Fe^{3+} and Tf-Al^{3+} in the brain for the Tf receptor; the second part was to determine that the ligands were, indeed, interacting with the same receptor. Tf-Al^{3+} and Tf-Fe^{3+} demonstrate that they are acting interchangeably with the same receptor; the interactions of both Tf-Al^{3+} and Tf-Fe^{3+} with the receptor are completely reversible over the time periods indicated [4].

Tf-Al^{3+} and Tf-Fe^{3+} have the same high affinity for the Tf receptor. Cells in the brain possess a specific high-affinity receptor for Tf that is independent of the metal being transported. The Tf-TfR system is postulated to be the prominent route whereby the brain can access iron from the general circulation to satisfy its high metabolic requirements. It is defined that about only 30% of the ion binding sites that plasma Tf has available in the circulation are saturated with iron at any time [5], leaving the remaining 70% available to other ions. Some analysis of batches of available "iron-saturated" Tf by this laboratory and others has also demonstrated that up to 30% of these binding sites are actually occupied by Al^{3+} [6]. Study has demonstrated that a metal ion other than iron is capable not only of binding to Tf but also of utilizing this interaction to gain access to cells in the brain via the Tf-TfR system. And Al^{3+} can enter into the brain though Tf-TfR system in a normal physiological path as the same cellular routes of Fe^{3+}.

Furthermore, Al^{3+} may be capable of interfering with normal cellular iron homeostasis and could disrupt iron-dependent cellular processes (e.g., oxidative phosphorylation) in the central nervous system. In this regard, studies have defined that ferritin isolated from the brains of Alzheimer's disease patients, which is the chief iron storage protein, has a sixfold higher Al^{3+}content than normal age-matched controls. Studies found that the binding activity of Tf increased significantly in Alzheimer's patients, and it also suggested that increasing of Tf-iron binding activity may also play a role in Al^{3+} entry into the brains of these patients [7].

3.1.1.3 Aluminum Citrate Enters into the Brain Mediated by Monocarboxylic Acid Transporters (MCTs), Which Is Also a Family of Transporters That Moves Monocarboxylic Acids Across Membranes

The presence of proton-coupled MCTs was first recognized by lactate and pyruvate transport into human red blood cells with transport being significantly inhibited by α-cyano-4-hydroxycinnamate. Currently, the family of transporters is defined that it contains 14 members, and 4 members (MCT1, MCT2, MCT3, MCT4) have been demonstrated to mediate the proton-dependent transport of monocarboxylates such as lactate, pyruvate, and ketone bodies. MCT8, earlier known as XPCT (X-linked PEST containing transporter) with 12 putative transmembrane domains, with both N- and C-terminal ends located on the inside of the plasma membrane, contains a PEST domain in its N-terminal and is a thyroid hormone transporter. Studies demonstrated that MCT8 transports both the thyroid hormones (T3 and T4) with high affinity with Km values of 2–5 μM. MCT8 is distributed extensively in many tissues including the heart, brain, pituitary, liver, kidney, skeletal muscle, and thyroid. MCT10 is an aromatic amino acid transporter and also is a T-type amino acid transporter1 (TAT1). The functional characterization of other members of this family has not been done and they are known as orphan transporters. MCTs have 12 transmembrane domains with C- and N-termini within the cytoplasm and an intracellular loop between TMDs 6 and 7. The conservation of sequence between different isoforms of the mammalian MCTs is the greatest for MCT1-4, whereas sequence is least conserved between other members of the family. The TMDs are highly conserved between the family members with high variations in the C- and N- termini including the intracellular loop. The variations in the sequences of different isoforms may lead to differences in substrate specificity and regulation of MCTs. The regulation of MCTs has been demonstrated to occur both by transcriptional and posttranscriptional mechanisms [8].

The MCTs have been found in the membranes of erythrocytes, the brain capillary endothelial cells that comprise the blood-brain barrier, and various other cells [9]. They can transport lactate and other monocarboxylates across mammalian plasma membranes. Its primary endogenous substrate is L-lactate; pyruvate, acetate, propionate, and butyrate are also substrates [10]. Valproate and salicylate are substrates for the blood-brain barrier MCT [11]. MCTs provide electroneutral cotransport of monocarboxylates along with protons in a stoichiometric ratio of 1:1, and the direction of transport is determined by the relative intra- and extracellular concentrations of monocarboxylates and hydrogen ions. As a transporter, the function of MCT1 is dependent on a proton gradient, and it acts as a proton-dependent cotransporter/exchanger. Transport followed an ordered, sequential mechanism. The first step is that a proton binds to the transporter and then binds to lactate. The second part is that the proton and lactate are further translocated across the membrane with their sequential release on the other side. The return of the free trans-

porter binding site across the membrane determines the net flux of lactate and thus forms the rate-limiting step of transport. Transport can be stimulated by a pH gradient (low to high). This may indicate either influx or efflux of substrate depending of the intracellular and extracellular substrate concentrations and the existing pH gradient across the plasma membrane.

It has been defined that aluminum citrate, which possesses a free monocarboxylic acid moiety, can be transported across the blood-brain barrier mediated by the MCT located [12]. Once aluminum enters the circulation, it is associated with several endogenous ligands. Two to four percent was bound to the small molecular weight ligand citrate except for 81% of aluminum in circulation which was coffiplexed with transferrin [13]. Other researchers demonstrated that 11% of the aluminum in serum is bound to citrate [14]. Aluminum citrates were the predominant aluminum species under the conditions employed. And the aluminum citrate complex is the predominant small molecular weight species found in serum. Aluminum is complexed to citrate by two of its three carboxylates and its alkoxy group, leaving a free carboxylate. Aluminum citrate transport across the blood-brain barrier involves either an uncharacterized monocarboxylate transporter MCT isoform expressed in the brain such as MCT7 or MCT8 or one of the many members of the organic anion transporting protein family, some of which are known to be expressed at the blood-brain barrier.

Many substrates and inhibitors of MCT1 and organic anion transporters, e.g., BSP and fluorescein, reduced aluminum citrate uptake into b. End5 cells which showed expression of MCT1, but not MCT2 or MCT4.

The process that aluminum cirate uptakes into the brain by MCTs depends on ATP [12]. The uptake of aluminum citrate can be reduced by inhibitors of mitochondrial respiration and oxidative phosphorylation. It suggested that it is an ATP-dependent mechanism. But it is not inhibited by ouabain, suggesting no role for Na/K-ATPase [12].

The aluminum citrate uptake through MCTs is sodium and pH independent [12]. Many members of the MCT appear to be sodium independent. And the uptake of aluminum citrate was pH independent. Citrate uptake increased at pH 6.9 compared to 7.4, whereas citrate uptake did not. At physiological pH, aluminum citrate is a better substrate if the uptake of aluminum citrate and citrate is mediated by the same carrier. The uptake of citrate enhancing at pH 6.9 may be due to reduce ionization of citrate. The lower pH increases the concentration of aluminum, which may serve as a better substrate for a monoanion carrier. The different response to pH reduction may show different transporters for citrate and aluminum citrate. Inhibition of aluminum citrate uptake by some compounds, e.g., furosemide which is a nonselective cation channel blocker, anion-exchange inhibitor and possible substrate for the MCT, and organic anion transporters, may reflect a requirement for another ion in the transport process but more likely reflect nonspecific effects [12].

3.1.1.4 Aluminum Citrate Enters into the Brain via System Xc–, Which Is Known to Be a Na^+-Independent Glutamate Transporter, at the BBB

System xc− or the cystine/glutamate antiporter is composed of transporter protein and a heavy chain subunit. The former is a light chain-specific subunit, xCT, which is encoded by the slc7a11 gene. The latter is a cell surface antigen protein 4F2hc that is encoded by the slc3a2 gene [15]. It exchanges glutamate for cystine in a 1:1 ratio and according to the respective concentration gradients [16]. Under physiological conditions, cystine is imported and intracellularly reduced to cysteine, a building block of the antioxidant GSH. In vitro, cystine supply via system xc− is very crucial for survival of certain cell types as they can only survive in the absence of system xc− when the medium is supplemented with reducing agents [17]. In vivo, however, it has been defined that genetic deletion of system xc− does not necessarily lead to any gross abnormality in the CNS, and there are no any signs of increased oxidative stress since GSH from other sources can be supplied by different cell types to sensitive cells [18]. While cystine is imported, glutamate is obligatorily exported, and system xc− has been identified as the major source of extracellular glutamate in several rodent brain regions [19]. Glutamate released via system xc− physiologically modulates synaptic transmission via activation of pre- and postsynaptic metabotropic glutamate receptors located in the vicinity of the synaptic cleft [16]. Moreover, studies have recently shown that the released of glutamate via system xc− regulates glutamatergic synapse strength through reducing the number of postsynaptic alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPA receptors). Additionally, this glutamate could also activate extrasynaptic N-methyl-D-aspartic acid receptors (NMDA receptors) and as such in high concentrations may induce excitotoxicity [16].

System xc− is a Na^+-independent glutamate transporter and an l-glutamate/l-cystine exchanger. It has been found that it widespread distributes in the brain [20]. System xc− is expressed at high levels in the brain parenchyma and the meninges and the ependyma. The central nervous system cell types contribute to system xc− activity in acute brain slices by cystine uptake or in living animals by microdialysis. It is showed that system xc−-dependent cystine uptake in microglia is higher than in astrocytes and neurons, microglia>astrocytes>neurons. Study has shown that system xc− activity in cortical astrocytes is higher compared to neurons and microglia. The activity of system xc− increased in microglia with sAPP, leading to compromised synaptic density in hippocampal neurons in co-culture.

System xc− transports an anionic form of l-cystine in exchange for l-glutamate. Studies have shown that aluminum citrate is transported by the same transporter, system xc−, as well as l-glutamate and l-cystine, at the BBB, in RBEC1 (a BBB model cell line). The Na^+-dependent uptake of aluminum citrate was shown in RBEC1. It suggested that Na^+-dependent transport systems such as the EAATs are

involved in the aluminum citrate uptake in RBEC1 [21]. System xc− activity is very important for maintenance of the intracellular glutathione level and the redox balance between cystine and cysteine in the extracellular milieu [22]. Under several inflammatory factors including LPS, oxidative stress, and TNFα can also activate or increase the expression of macrophage/microglial system xc− [23]. Possible physiological roles for the induction of system xc− are acting as a detoxifying system in the brain and BCEC1 by supplying l-cystine/l-cysteine from the circulating blood for the synthesis of glutathione. Therefore, chronic inhibition of system xc− at the BBB by its blockers and/or substrate inhibitors such as aluminum citrate is speculated to cause decreases in the l-cystine levels in BCEC1 and the brain, and then vulnerability of the BCEC1 and neurons to oxidative stress, resulting in BBB dysfunction and neurodegenerative diseases [24]. Such a process is consistent with the direct demonstration that depletion of glutathione in primary murine cortical cells enhances the extent of NMDA-mediated excitotoxicity.

Aluminum citrate can be taken up into RBEC1 via system xc−, so this system might play an important role in aluminum citrate transport at the BBB. The uptake of aluminum citrate showed temperature and concentration dependency, and it did not require an inwardly directed Na^+-gradient as a driving force, ruling out the involvement of Na^+-dependent glutamate transporters in its transport [21].

3.1.2 Aluminum-Containing Compounds Could Enter into the Brain Through the Olfactory Mucosa/Olfactory Bulb Barriers

The three rabbits, which remained free of neurological deficits, are exposed to aluminum lactate through the nasal cavity. There are granulomas in the left olfactory bulb and cerebral cortex. The cortical involvement was bilateral but more severe on the left. Two animals had granulomas in the pyriform cortex and one had a lesion in the hippocampus. The granulomas consisted of accumulations of macrophages, lymphocytes, and occasional plasma cells. A granuloma was identified within the fiber layer of the left olfactory bulb of one of the animals receiving Al chloride, but granulomas were not seen in the cerebral hemispheres of these animals. The animals exposed to sodium lactate were free of comparable lesions; the result indicated that aluminum lactate could enter into the brain through olfactory mucosa/olfactory bulb barriers [25].

Aluminosilicates comprise the bulk of inhaled aerosol contaminants in the air. Aluminum-containing compounds could enter into the brain through olfactory mucosa/olfactory bulb barriers under physiological conditions and a defect in the normally very effective olfactory mucosa/olfactory bulb barriers leading to excessive influx into the brain of aluminum-containing compounds.

3.1.3 Little Aluminum Enters the Brain Through Choroid Plexus

Although metals could enter the brain across the choroid plexus, it is not a prominent way for aluminum entering the brain. There is a choroid plexus in each of the four cerebral ventricles of the brain. They synthesize most of the cerebrospinal fluid (CSF) that fills the brain ventricles and the subarachnoid space that surrounds the brain and spinal cord. The total surface area of the choroid plexuses is approximately 10cm^2. About 1/1000 of the surface area of brain capillaries are the site of the BBB. Brain atlases of the rat and human show brain regions as far as 1 mm away from the nearest component of the CSF. There is little opportunity for the choroid plexuses and CSF compartment than through rapid exchange between blood, and the brain through the BBB aluminum citrate was administered via the femoral vein. Peak aluminum concentrations were seen within the first 10 min at all three sites, the frontal cortical brain, blood, and lateral ventricle. Aluminum frontal cortical brain/blood ratios (oBBRs) were significantly higher than those for the lateral ventricle. The result suggested that the primary site of aluminum permeation across the BBB is at cerebral capillaries [26]. So, aluminum primarily enters the brain from blood through the BBB rather than through the choroid plexuses, and little aluminum enters the brain through choroid plexus.

3.2 Aluminum Effluxes from the Brain

Study has showed that aluminum can be remove from brain ECF, either into brain cells or blood through a carrier, and it is effective and energy-dependent [26]. But more researchers defined brain entry of aluminum, presumably from blood, and some degree of aluminum persistence in the brain. The redistribution of aluminum out of the brain is slow. The concentration of aluminum in human brain increases with age. The half-life of brain aluminum could not be accurately calculated but was estimated to be about 150 days [2].

Researchers observed that rat brain aluminum concentrations decreased only slightly from 1 to 35 days after systemic aluminum injection, in the absence or presence of the aluminum chelator desferrioxamine. It suggested that aluminum could be retained in the brain for a long time. Part of aluminum flows out the brain across the BBB shortly after the aluminum enters the brain. But once aluminum enters the cells, it may be retained for a long time [27].

3.3 The Influence Factors of Aluminum Entry and Deposition in the Brain

3.3.1 Parathyroid Hormone (PTH) and Vitamin D

Some studies defined that in individuals with normal renal function, PTH and vit D can promote the absorption of aluminum in the liver, brain, and parathyroid [28].

3.3.2 Permeability of the BBB

The primary lesion in Alzheimer's disease and dialysis dementia has been postulated to be an impaired BBB permeability that allows neurotoxins like aluminum to reach the central nervous system. Actually aluminum itself affects the permeability of the BBB of rats to small peptides. Intraperitoneal injection of aluminum chloride increased the permeability of the BBB to iodinated N-Tyr-delta-sleep-inducing peptide and beta-endorphin by 60–70% [29]. The results of immunohistochemistry and Western blot analysis showed that aluminum induced a decrease in the expression of F-actin and occludin. All these results suggested that aluminum toxicity might be related to the change of the permeability and the integrity of BBB [30].

Short time and low dose of aluminum might not change the ability of learning and memory in juvenile rats; however, the permeability and ultrastructures of the BBB might be significantly changed [31].

Aluminum chloride and aluminum lactate can increase the permeability of the blood-brain barrier, while aluminum hydroxide can gradually increase the concentration of human or animal blood aluminum after prolonged and repeated consumption [32]. It increases the rate of transmembrane diffusion and selectively changes saturable transport systems [33].

So aluminum can increase permeability of the BBB, and then more aluminum enters the brain.

3.3.3 Citric Acid

Study has defined concentrations of aluminum in the cerebral cortex, hippocampus, and cerebellum of rats which were treated with 100 mg aluminum/kg body weight in the form of aluminum citrate. And aluminum concentrations in the cerebral

cortex in the animals fed citric acid increased because of possible absorption of the citrate chelate presumably formed with the aluminum present in the diet. But there was no significant increase in tissue aluminum concentrations in all brain regions in Sprague-Dawley or Wistar rats after treatment with aluminum hydroxide. It suggested that citric acid can promote influx of aluminum into the brain [34].

Aluminum, as a known neurotoxicant, can enter the brain through BBB, the choroid plexuses, and sensory nerve from the nasal cavity, but the efflux of aluminum from brain is very slow. So aluminum can be deposited in brain for a long time, then it is a main reason which induces neurotoxicity. Some compounds of aluminum can injure BBB, through which the raising of the blood-brain barrier permeability can promote aluminum to enter into the brain.

References

1. Yokel RA (2002) Brain uptake, retention, and efflux of aluminum and manganese. Environ Health Perspect 110(Suppl 5):699–704
2. Levin VA (1980) Relationship of octanol/water partition coefficient and molecular weight to rat brain capillary permeability. J Med Chem 23:682–684
3. Daniels TR, Delgado T, Rodriguez JA, Helguera G, Penichet ML (2006) The transferrin receptor part I: biology and targeting with cytotoxic antibodies for the treatment of cancer. Clin Immunol (Orlando, Fla) 121:144–158
4. Roskams AJ, Connor JR (1990) Aluminum access to the brain: a role for transferrin and its receptor. Proc Natl Acad Sci U S A 87:9024–9027
5. Cochran M, Coates J, Neoh S (1984) The competitive equilibrium between aluminium and ferric ions for the binding sites of transferrin. FEBS Lett 176:129–132
6. Trapp GA (1983) Plasma aluminum is bound to transferrin. Life Sci 33:311–316
7. Farrar G, Altmann P, Welch S, Wychrij O, Ghose B, Lejeune J et al (1990) Defective gallium-transferrin binding in Alzheimer disease and down syndrome: possible mechanism for accumulation of aluminium in brain. Lancet 335:747–750
8. Vijay N, Morris ME (2014) Role of monocarboxylate transporters in drug delivery to the brain. Curr Pharm Des 20:1487–1498
9. Conn AR, Fell DI, Steele RD (1983) Characterization of alpha-keto acid transport across blood-brain barrier in rats. Am J Phys 245:E253–E260
10. Oldendorf WH (1973) Carrier-mediated blood-brain barrier transport of short-chain monocarboxylic organic acids. Am J Phys 224:1450–1453
11. Terasaki T, Takakuwa S, Moritani S, Tsuji A (1991) Transport of monocarboxylic acids at the blood-brain barrier: studies with monolayers of primary cultured bovine brain capillary endothelial cells. J Pharmacol Exp Ther 258:932–937
12. Yokel RA, Wilson M, Harris WR, Halestrap AP (2002) Aluminum citrate uptake by immortalized brain endothelial cells: implications for its blood-brain barrier transport. Brain Res 930:101–110
13. Harris WR (1992) Equilibrium model for speciation of aluminum in serum. Clin Chem 38:1809–1818
14. Ohman LO, Martin RB (1994) Citrate as the main small molecule binding Al3+ in serum. Clin Chem 40:598–601
15. Sato H, Tamba M, Ishii T, Bannai S (1999) Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. J Biol Chem 274:11455–11458

16. Massie A, Boillee S, Hewett S, Knackstedt L, Lewerenz J (2015) Main path and byways: non-vesicular glutamate release by system xc(-) as an important modifier of glutamatergic neurotransmission. J Neurochem 135:1062–1079
17. Sato H, Shiiya A, Kimata M, Maebara K, Tamba M, Sakakura Y et al (2005) Redox imbalance in cystine/glutamate transporter-deficient mice. J Biol Chem 280:37423–37429
18. Massie A, Schallier A, Kim SW, Fernando R, Kobayashi S, Beck H et al (2011) Dopaminergic neurons of system x(c)(-)-deficient mice are highly protected against 6-hydroxydopamine-induced toxicity. FASEB J 25:1359–1369
19. De Bundel D, Schallier A, Loyens E, Fernando R, Miyashita H, Van Liefferinge J et al (2011) Loss of system x(c)- does not induce oxidative stress but decreases extracellular glutamate in hippocampus and influences spatial working memory and limbic seizure susceptibility. J Neurosci 31:5792–5803
20. Bassi MT, Gasol E, Manzoni M, Pineda M, Riboni M, Martin R et al (2001) Identification and characterisation of human xCT that co-expresses, with 4F2 heavy chain, the amino acid transport activity system xc. Pflugers Archiv 442:286–296
21. Nagasawa K, Ito S, Kakuda T, Nagai K, Tamai I, Tsuji A et al (2005) Transport mechanism for aluminum citrate at the blood-brain barrier: kinetic evidence implies involvement of system Xc- in immortalized rat brain endothelial cells. Toxicol Lett 155:289–296
22. Danbolt NC (2001) Glutamate uptake. Prog Neurobiol 65:1–105
23. Hosoya K, Tomi M, Ohtsuki S, Takanaga H, Saeki S, Kanai Y et al (2002) Enhancement of L-cystine transport activity and its relation to xCT gene induction at the blood-brain barrier by diethyl maleate treatment. J Pharmacol Exp Ther 302:225–231
24. Schulz JB, Lindenau J, Seyfried J, Dichgans J (2000) Glutathione, oxidative stress and neurodegeneration. Eur J Biochem 267:4904–4911
25. Perl DP, Good PF (1987) Uptake of aluminium into central nervous system along nasal-olfactory pathways. Lancet 1:1028
26. Allen DD, Yokel RA (1992) Dissimilar aluminum and gallium permeation of the blood-brain barrier demonstrated by in vivo microdialysis. J Neurochem 58:903–908
27. Yokel RA, Allen DD, Ackley DC (1999) The distribution of aluminum into and out of the brain. J Inorg Biochem 76:127–132
28. Ott SM (1985) Aluminum accumulation in individuals with normal renal function. Am J Kidney Dis 6:297–301
29. Banks WA, Kastin AJ (1983) Aluminium increases permeability of the blood-brain barrier to labelled DSIP and beta-endorphin: possible implications for senile and dialysis dementia. Lancet 2:1227–1229
30. Song Y, Xue Y, Liu X, Wang P, Liu L (2008) Effects of acute exposure to aluminum on blood-brain barrier and the protection of zinc. Neurosci Lett 445:42–46
31. Liu X, Liu LB, Liu YH, Xue YX (2008) Effects of aluminum on the integrity of blood brain barrier in juvenile rats. Zhonghua yu fang yi xue za zhi [Chin J Prev Med] 42:12–15
32. Wen GY, Wisniewski HM (1985) Histochemical localization of aluminum in the rabbit CNS. Acta Neuropathol 68:175–184
33. Banks WA, Kastin AJ (1989) Aluminum-induced neurotoxicity: alterations in membrane function at the blood-brain barrier. Neurosci Biobehav Rev 13:47–53
34. Slanina P, Falkeborn Y, Frech W, Cedergren A (1984) Aluminium concentrations in the brain and bone of rats fed citric acid, aluminium citrate or aluminium hydroxide. Food Chem Toxicol 22:391–397