Iron and Aluminum Homeostasis in Neural Disorders

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The brain is the most compartmentalized organ. It is also highly aerobic. Because nerve cells grow but do not regenerate, the brain is the organ best suited for the accumulation of metabolic errors colocalized in specific areas of the brain over an extended period. Alzheimer’s disease (AD) is primarily a neurological disorder of the elderly. It is suggested that this disorder results from the accumulation of such errors, and that AD onset aluminum and iron contribute to but do not necessarily initiate the onset of the disease. 

Introduction

Alzheimer’s disease (AD) is an age-associated dementia characterized by altered memory, cognition, and behavior. In AD, nerve cells in the specific areas of the brain degenerate. Theories contributing to AD include decreased cholinergic innervation, defective protein synthesis, defective protein turnover, and aluminum toxicity (1). None are unequivocally proved or ruled out. Indeed, to date, the observed differences in normal and AD brain are quantitative rather than qualitative, but a search for a single biochemical event initiating AD has been unsuccessful. This is true even of the most current suspect, the amyloid plaques; the aggregates of the β-amyloid peptides (β-AP) generated by the proteolysis of the β-amyloid precursor proteins (β-APPs) (2).

An adult brain weighs between 1.2 and 1.5 kg, but utilizes 20% of the oxygen consumed by the body. This highly aerobic tissue uses glucose as a sole or major source of energy. The requirement for glucose is very high—120 g/day, compared to 190 g for the entire body (3). The brain is also a highly compartmentalized organ; the use of glucose is area specific and stimuli dependent. For example, the areas of the brain using glucose in response to visual stimuli are distinct from those using glucose in response to auditory stimuli (4). Furthermore, unlike other tissues, brain cells do not multiply or regenerate. Thus, this vital organ is also well suited for the accumulation of toxins such as aluminum and also of metabolic errors which may result from such accumulation.

Solution chemistry of aluminum is quite complex. Martin has suggested that Al(III) is the biologically relevant species and, based on its affinity constants for citrate and transferrin as well as their circulating concentrations in vivo, these two compounds are primarily responsible for the chelation and transport of aluminum (5). Regardless of the vehicle used for transporting aluminum, it is generally agreed that the concentration of aluminum in AD brains is high and that the distribution of aluminum within the brain is nonuniform (6–8). Despite highly sensitive techniques for quantifying focal concentrations of brain aluminum, some researchers dispute the role of aluminum in AD and some dispute even the elevated levels of aluminum in AD brains (9). Nevertheless, several reports acknowledge that aluminum may play a role in AD (10).

We hypothesized that a critical mass of metabolic errors colocalized in specific areas of the brain is essential to produce a neurological disorder such as AD. Aluminum, a recognized neurotoxin, participates in formulating this critical mass by interfering in the metabolism of glucose, iron and proteolytic processing of β-APPs. Evidence obtained in our laboratory supports this hypothesis. It is summarized below.

Aluminum and Glucose Metabolism

Glucose enters glycolysis as glucose-6-phosphate (G6P). This reaction, catalyzed by hexokinase, requires ATP and Mg(II). In the brain, the enzyme is membrane bound and the activity is latent. The activation requires its release from the membrane. This then is the first step in glucose consumption. Aluminum (III) binds to ATP 10 times more tightly than does Mg(II). Thus, in vitro, the concentration of aluminum as low as 160 nM inhibits hex-

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Thus,unlikehexokinase,aluminumbound

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Inthebrain,theshutt pathwayis

associatedalmostexclusivelywithmyelinated
tissue,andeveryactivity

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(15).Because

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synthesisoffattyacidsrequiresnADPH,

thiscloseassociationisfunctionallyadvantageous.

The rate-limiting step in glycolysis is the
modulation of phosphofructokinase and
fructose-1,6-bisphosphatase activities
by fructose-1,6-bisphosphate, ATP, and
fructose-2,6-bisphosphate. However, recent
studies have shown that in the brain, the
initialmodulatorisribose-1,5-bisphosphate
(16).Reducedsupplyofribose-5-
bisphosphate resulting from the aluminum-
mediated reduction in production of
NADPH and ribose-5-phosphate would
produceafocelefficientofthekycomponent
essentialformyelinsynthesisaswell
asforregulationofglycolysis.

Experimentalmetaltoxicitycanbe
producedbyinjectingveryhighconcentra-
tions of the toxicant. While such studies
save time, physiologically relevant metal
toxicity results from prolonged exposure to
a chronic level of the toxicant. We reported
that brain homogenates of rats fed 100 μM
AlCl3·6H2O in the drinking water for 1
year had about a 25% reduced activity of
hexokinase and G6PD (17). Examination
of the sections of the brains of rats similarly
exposed to AlCl3·6H2O for two years also
showed between 15% and 20% reduction
of glucose metabolism in several areas of
the brain (18). The results approached sta-
tisticalsignificanceonlyforventral

lumadandtemporalcortex.Although

moreanimalswereessentialtoestablisha

statisticallysignificantdifference,the

observedreductioniscompatiblewith

thereportedaluminum-mediatedimpaired
metabolismofglyceratbrainsinvitro

(19)andreducedhexokinaseinADbrains

Iron and Brain Metabolism
In higherorganisms,ironboundto
transferrinandstoredin ferritin accounts
formorethan90%ofthenonhemeiron
(21).Bothproteinsalsosequisterother
metalions,includingaluminum(22).
Intracellularconcentrationofironregulates
thesynthesisofferritinandthestability
of the transferrin receptors. When the cellular
concentration of iron is high, the available
ferritinmRNAisutilizedmoreefficiently
and at lower concentrations of iron, the
transferrin receptor mRNA is more stable;
and,therefore,moretransferrinreceptors
areavailableforirontransport Thister-
igationis due to a conservedsequenceof28
nucleotidesatthe5'translatedregion
(5'-UTR)offerritinmRNAandatthe3'-
UTRofthetransferrinreceptor(23).
Transferrin(s), a family of glycoproteins of mw 80,000 is a single polypeptide chain. It has two metal-binding sites, one each at the N- and C-terminal end. It is the major serum protein that transports iron. It also binds other metal ions including aluminum (24,25). The stability constants for the N- and C-sites are not identical. In vivo, even under extreme iron overload, only 30% of the total iron binding sites are occupied by iron (21). Because a convenient radioactive isotope of aluminum is not available in vitro, radioactive gallium, $^{67}$Ga(III), is often used as an aluminum mimic and the data extrapolated to in vivo situations. Farrer et al. showed that transferrin from the sera of AD patients bound less gallium (and, therefore, less aluminum by inference) than the age-matched controls. They suggested that in AD patients transferrin binds less aluminum and, therefore, more serum aluminum is available for transport to the brain (26). This potentially attractive idea is controversial because the same observed reduced gallium binding would result if the presumed iron-free sites were actually occupied by aluminum. Furthermore, the more recent data suggests that in vivo aluminum and gallium are not transported by the same mechanism (27).

In this respect, the data by Connor et al. are noteworthy (28). These workers showed that the access of aluminum to various areas of the brain is probably via the transferrin-mediated receptor system; they suggested that this system may also regulate the transport of other metal ions. They also noted that although transferrin and its receptors are present throughout the brain, their distribution in the central nervous system is not uniform (28). These observations further underscore the possibility of a colocalization of metal ions producing metabolic errors leading to neurological disorders.

Transferrin in the serum delivers its metal ions to the brain via a transferrin-receptor mediated system. The olfactory system seems to have its own transferrin-like protein, thus gaining direct access to the brain (DP Perl, personal communication). In the brain, iron and presumably other metal ions are sequestered by ferritin.

**Aluminum, Iron, and Ferritin in the Brain**

In humans, most of the iron is recycled and very little is excreted. Therefore, the concentration of total iron in the human body increases with age (29). In the male, it increases from about 300 mg at age 20 to 25 years to about 1800 mg at age 80 to 90 years. In the female, the levels remains at about 300 mg until the years of age 50 or until menopause, and increase to about 1200 by the age of 80 to 90 years. Significantly, a fetal brain has very little iron or ferritin which stores it. In the adult brain, a third of the total noneheme iron is stored in ferritin (30). This protein is composed of a total of 24 chains, heavy (H) and light (L), of molecular weights of 21,000 and 19,000, respectively. A fully saturated ferritin can store in its protein shell up to 4500 molecules of iron as Fe(III) hydroxypophate. Isoferritins varying in subunit composition exist in different tissues. Ferritin binds several metal ions in vitro and in vivo. Indeed, ferritin aluminum complex can be prepared in vitro, and has been isolated from the brains of two AD patients and from rats chronically exposed for a year to 100 μM AlCl$_3$·6H$_2$O in their drinking water (31). Our subsequent studies (unpublished data) showed that ferritin isolated from two AD and one normal brain had between 2 and 4 moles of aluminum bound per mole of protein, and one AD brain ferritin had 12.8 molecules of iron per mole of ferritin. In all AD brains, the concentration of ferritin was consistently higher than in the controls. Cochran and Chawtur (32) also observed similar binding of aluminum to ferritin in vitro. In contrast, Deadman et al. (33) could not observe any difference in the aluminum bound to ferritin in normal and AD brains, but consistent with earlier observations (31) reported elevated levels of ferritin in AD brains and they produced aluminum ferritin complexes in vitro. We observed that in vitro more aluminum bound to holoferritin than to apo ferritin and that aluminum reduced the rate of iron uptake by ferritin (34).

To determine whether human brain ferritin is chemically distinct from that found in the liver, we undertook further characterization of human brain ferritin and its subunits. SDS-PAGE of ferritin from normal or AD brain showed two bands, H = 70%, L = 30%. However, isoelectrofocusing on native ferritin showed several bands of isoferritins (31). HPLC chromatography (35) of human brain ferritin from normal or AD tissues yielded a cluster of about five heavy chains and predominantly only one light chain (Figure 2). This appeared to have offered an explanation for several isoforms of brain ferritin resolving after isoelectrofocusing of the native protein. To determine the difference, if any, in the amino acid sequences of H chains, we used a cDNA clone for ferritin heavy chain from the liver and screened the human brain cDNA libraries from 11 week old fetal brain and from adult normal and AD brains. The cDNAs isolated from these sources were sequenced by the "dideoxynucleotide" method. The preliminary results schematically represented in Figure 3 show several things:
Figure 5. Aluminum trichloride activates bovine pancreas α-chymotrypsin 2-fold at pH 6.5. The inset is a Lineweaver-Burke plot with a $K_{\text{cat}}$ for aluminum trichloride of $2 \times 10^{-3}$ M. The shaded points are those used for the $K_{\text{cat}}$ determination. Standard assay conditions [39] were used, except 38 mM PIPES buffer, pH 6.5, was employed, the methanol concentration was reduced to 3%, and calcium chloride was absent from the control assays. Fresh solutions of Sigma enzyme were made daily, calibrated for activity, and kept in dilute HCl on ice to prevent autoxidation. One-min preincubations of metal and enzyme were shown to be sufficient for full activation. The synthetic substrate, benzoyl-tyrosine ethyl ester (BTEE), was not precipitated or hydrolyzed by the addition of aluminum trichloride alone. Different orders of addition did not affect activation [39].

* none of these cDNAs were full length at the 5’ end.
* Northern blot analysis of the RNA (poly A+) preparations from human liver, normal adult and AD brain and 11-week-old fetal human brains revealed the presence of two transcripts of 1.4 kb and 1.1 kb for ferritin.
* The larger, 1.4 kb, is most abundantly expressed in the brain, while its level of expression in the liver is 10 times lower.
* The two transcripts are also expressed differentially in other human tissues like kidney, lungs, pancreas, heart, placenta, and skeletal muscle.
* Comparison of the sequence showed that the small transcript (1.1 kb) from the brain was identical to that reported in the liver.
* The larger transcripts (1.4 kb) were incomplete at the 5’ end but contained a 279 sequence at 3’-UTR which is absent from the smaller transcript.
* Computer comparisons of the 279 bp sequence with the GenBank and EMBL databases showed it to be 94.1, 62.5, and 58.9% homologous to the ferritin heavy chain genomic sequences of human, mouse and rat, respectively [36]. However, in all these cases, it is reported to be the part of the nontranscribed region.
* Northern blot hybridization and computer analysis of the sequences of 1.4 kb RNAs suggests that the 279 bp DNA fragment corresponds to the mature ferritin mRNA.
* It is especially noteworthy that the fetal brain cDNA (1.6 kb) and the adult brain cDNA (1.4 kb) are identical at the 3’-UTR and identical to the available sequence of the coding region.
* The fetal brain cDNA is identical to the liver (1.1 kb) cDNA in the coding region and only a part of 5’ UTR. However, the presence of a stretch of 28 nucleotide sequence in the S’UTR corresponding to the iron responsive element in the liver mRNA could not be detected in the fetal brain mRNA. Instead, a different =54 nt sequence is observed. Whether this belongs to the ferritin mRNA or to a totally unrelated gene and the role of 279 bp sequence in the regulation of ferritin synthesis is under investigation.

**Aluminum and Plaque Formation**

Presence of plaques in an AD brain first discovered by Alzheimer in 1907 [37] has survived the test of time and is now considered a histopathological benchmark of the AD brain. The plaques are aggregates of a 39 to 42-amino-acid-long peptide (β-APP) produced by the proteolysis of a family of α-amyloid precursor proteins (β-APPS). Serine proteases are suggested to be involved in this processing. Part of the β-A4 segment of β-APP is lodged in the plasma membrane that separates cytoplasm from the extracellular region (Figure 4). These proteins are also found in other nor-

**Figure 6.** Aluminum protects α-chymotrypsin from inhibition by bPTI and BX-9 to a similar extent. The abscissa gives the concentration of either bPTI or BX-9 inhibitor. The inset shows an enlargement of the inhibition curve for the control enzyme ($1.75 \times 10^{-3}$ M) with bPTI (●) or BX-9 (●). In the presence of $5 \times 10^{-4}$ M Al, the inhibition constant ($K_i$) for bPTI (●) and for BX-9 (△) were approximately 100-fold higher. The $K_i$ values were calculated as published by Sinha et al. [47]. The profiles of the control curves were similar to those previously reported, but not all of the BX-9 reacted to form inhibitor–protease complex. This was also seen in part in the original work on BX-9 [47]. This may simply relate to the presence of the β-galactosidase portions of the fusion protein. However, an altered binding mechanism at the acidic pH cannot be excluded [39].
Aluminum also activated trypsin by 140% with a similar $K_\text{m(app)}$ but produced only a 15-fold decrease in the binding of bPTI (data not shown). In addition to $\alpha$-amyloid peptide(s), AD plaques also contain $\alpha$-1-antichymotrypsin. Aluminum protected against inhibition by $\alpha$-1-antichymotrypsin, but the change in $K_i$ was only about 10-fold. The above results were obtained with synthetic substrates. To verify whether the results hold true for natural substrates, we studied limited proteolysis of transferrin by $\alpha$-chymotrypsin in the presence of AlCl$_3$•6H$_2$O. Indeed, aluminum produced a 2-fold increase in the rate of proteolysis of transferrin ($K_\text{m(app)}$—2.1 × 10$^{-4}$ M). Finally, 100,000 g supernatants of brain homogenates at pH 6.5 also showed a 2.8-fold increase in the rate of hydrolysis of BTEE in the presence of 5 × 10$^{-4}$ M AlCl$_3$•6H$_2$O.

**Role of Iron in Plaque Formation**

Interaction of metal ions such as Fe(II) with oxygen produce oxygenated free radicals (42). These radicals oxidatively modify proteins and make them more susceptible to proteolysis (43), damage DNA, and peroxidize lipids (42). Aluminum enhances the lipid peroxidation of erythrocyte membranes initiated by iron. The rate of this lipid peroxidation is greater at acidic pH (44). Acidic pH also accelerates the rate of the release of iron from ferritin (21) and favor aggregation of $\beta$-AP (45). More recently Dyet et al. (46) reported that in vitro, the cross-linking of $\beta$-AP, which causes the formation of insoluble plaques, is enhanced by oxygenated free radicals produced in the presence of a metal ion such as iron. Localized acidosis in the brain has been reported during ischemia, and hypoxia, and in AD patients (47–49). Figure 7 shows how these factors can contribute to plaque formation.

The role of aluminum and iron in deregulating brain metabolism discussed above is summarized in Figure 8. Almost all the changes observed in AD brain are quantitative and not qualitative. Thus, although the presence of increased aluminum in AD brain is generally confirmed, in one recent report its presence in AD (senile) plaques has been attributed to experimental artifact (50). Similarly, the presence of an increased concentration of ferritin in AD brain reported earlier (31,33) and its localization in neuritic plaques of AD patients (51) has been con-

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**Figure 7.** Working model showing the role of aluminum, iron, acidic pH, and proteases and their inhibitors in plaque formation (39).

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**Figure 8.** Schematic model of possible interactions and ill effects of iron and aluminum in brain metabolism.

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**Figure 6** shows the effect of bPTI or the bPTI-like segment of $\beta$-APs on the activity of $\alpha$-chymotrypsin and compares it with that of the aluminum-activated enzyme. As seen, aluminum dramatically protected $\alpha$-chymotrypsin against the inhibition by bPTI or the BX-9 fusion protein (41) which contains the bPTI-like segment of $\beta$-APP inserted into $\beta$-galactosidase. Aluminum reduced the affinity of either inhibitor for the enzyme by 100 fold ($K_i$ without Al = 3.7 × 10$^{-10}$ M, $K_i$(Al) = 4.6 × 10$^{-8}$ M).

Aluminum also activated trypsin by 140% with a similar $K_\text{m(app)}$ but produced only a 15-fold decrease in the binding of bPTI (data not shown). In addition to $\alpha$-amyloid peptide(s), AD plaques also contain $\alpha$-1-antichymotrypsin. Aluminum protected against inhibition by $\alpha$-1-antichymotrypsin, but the change in $K_i$ was only about 10-fold.

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firmed, but its association with AI was not seen in several AD brains (33). Most reports show that familial cases of AD once considered due to genetic mutations in the AD-gene in chromosome 21 may also arise from mutations in chromosomes 19 and 14 (52). The amyloid plaque unique for AD brains is observed by histopathologic examination of the brains of diseased patients and, therefore, has been considered by many as the end result, rather than the cause, of AD. The β-APPs exist in normal individuals also, but their biological function is unknown. Finally, even in the familial AD, identical afflicted twins are not affected by AD simultaneously. Similarly, not every individual exposed to elevated levels of environmental aluminum suffers from AD. It therefore appears that AD probably results from the iron-and aluminum-mediated colocalization of metabolic errors accumulating in specific areas of the brain (Figure 7). Clearly, the reactions shown do not have to occur in the order given. For example, large concentrations of β-AP can be produced with an active protease and sufficiently high concentrations of β-APPs. Aluminum, iron, oxygen, and an acidic pH can help achieve that level of β-AP faster and at lower concentration of β-APPs by activating the protease, and permitting its function despite the presence of the BPTI-like inhibitor of β-APPs and crosslinking β-AP. Similarly, the role of aluminum in deregulating various metabolic reactions in Figure 8 (12) as well as numerous others (10) could occur only if the local concentrations of aluminum and iron are sufficiently high. The same is true for the ill effects of unsequestered iron. Although the data presented above and summarized in Figures 7 and 8 have been obtained in vitro and need to be verified in vivo, recent reports seem to support the postulate that indeed iron and aluminum contribute to the onset of AD. Accordingly, epidemiologic studies of McLachlan et al. (53) reported partial relief against AD by desferrioxamine. This compound was first used against dialysis dementia caused by aluminum toxicity. It is an effective chelator for aluminum as well as iron. Thus, the observed relief against AD (53) may well be due to the removal of both these neurotoxins.

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