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# Reevaluating the role of amyloid $\beta$ -peptides in Alzheimer's disease: from pathogenic agents to protective chelation mechanisms

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Alzheimer's disease (AD) is a multifaceted neurodegenerative disorder with complex etiology, often associated with histological markers of oxidative stress, inflammation, and disturbances in calcium homeostasis. Traditionally, amyloid  $\beta$ -peptides ( $A\beta$ ) have been considered key contributors to these pathological processes. However, emerging evidence suggests a protective role for  $A\beta$  and the enzymes involved in its production. This article further explores the hypothesis published by us a decade before that posits amyloid  $\beta$ -peptides and the  $\beta$ -secretase enzyme (BACE1) are part of an intentionally designed cellular defense mechanism against metal toxicity. This challenges the conventional understanding of their roles in AD pathogenesis. It is not until this BACE1 system, primarily the associated amyloid plaque deposit sites, are saturated with heavy and other metals and the exposure to these cations continues to influx oxidative ions into the brain, do the indications of neurodegeneration begin to become symptomatic. Until this metal oversaturation takes place, the system –  $A\beta$  and the enzymes involved in its production and conveyance – keeps the oxidative potential of the metal toxins sequestered extracellularly and out of the way of the neuron's intracellular activities.

## KEYWORDS

Alzheimer's disease, amyloid  $\beta$ -peptides, BACE1, heavy metal toxicity, oxidative stress, neuroprotection, tau hyperphosphorylation, neurodegeneration

## Introduction

Alzheimer's disease (AD) is characterized by progressive neurodegeneration and cognitive decline, with a significant increase in prevalence expected in the coming decades. Current models primarily implicate amyloid  $\beta$ -peptides ( $A\beta$ ) in the disease's progression, associating them with various cellular dysfunctions such as oxidative stress, inflammation, and calcium dysregulation (1, 2). The enzyme  $\beta$ -secretase (BACE1), responsible for cleaving amyloid precursor protein (APP), has been viewed as a pathological driver in this context (3–5). However, this article expands on our previously published papers (6, 7) proposing a novel perspective; positioning  $A\beta$  and BACE1 as protective countermeasures against heavy and other metal toxicity. In this brief article we expand on the original proposal to dive deeper into the mechanism tied to the amino acid sequence of the  $A\beta$  peptide; a sequence that varies and whose functionality varies based on the different cleavage points by different enzymes. We attempt to show here how these different amino acid sequences relate to metal chelation and hydrophobic moieties that facilitate intercellular amyloid plaque formation. In the proposed paradigm, this biological activity to sequester the dangers of the highly oxidative metals is an intended design.

The brain represents approximately 2% of the body's weight but uses as much as 20% of the body's oxygen consumption (8). In addition, the density of the polyunsaturated fat and cholesterol mass in the membranes of the 100 trillion brain cells and the associated myelin is intensely more than that which we find in the cells of the rest of the body (7). The brain can house as much as

25% of the body's cholesterol (8), yet again it represents only 2 % of the body's mass. These concentrated substrates (and structural components) can be highly vulnerable to oxidation as they neutralize free radical stress (9) in the brain where oxygen consumption is at such high rates. The polyunsaturated fatty acid-rich environment of the brain, mainly arachidonic acid and docosahexaenoic acid is critical to more than just membrane structure. They are critical components of signaling mechanisms, synaptic function, neurogenesis and more (10). These polyunsaturated fats have a profound influence on brain function and are implicated in mood disorders, depression, bipolar, schizophrenia, attention deficit hyperactivity disorder and also AD (11). Research also irrefutably demonstrates that oxidation of these fats or other alteration of their chemistry results in altered signaling that circles back to implications related to all these behaviors as well as structure and function disorders, including AD (10).

As such, with this density of 'volatile fuels' that are vulnerable to oxidation in an environment that is exposed to an extraordinary oxygen burden, we would expect extraordinary precautions are naturally inbuilt to protect the tissues and interactions from this vulnerability. BACE1 activity is directly related to escalated inflammatory activity – NF- $\kappa$ B signaling (12–14). This may be a designed protective response to inflammation exacerbated by oxidation which itself is facilitated by the Fenton reaction or oxidative activity facilitated by other cations. Oxidation promotes inflammation and vice versa (15, 16). The BACE1 activity may not at all be nefariously pathological. It is more likely protective as it generates the unique A $\beta$  peptide described in detail in Figure 1 with a greater capacity to chelate, capture and sequester the danger that these metals represent to this highly volatile environment in the brain. It should be expected that the highly vulnerable conditions of the structural and signaling components in the brain are at incremental risk due to the enhanced metabolic activity of the neuron and the dependence on higher oxygen consumption than anywhere else in the body.

While the BACE1 system can provide compensatory protection, persistent exposure to these metals eventually overwhelms the successful countermeasure and in due time, collapse of the protective

mechanism results in disease. Heavy metals seem to play a pivotal role in this context. Upon analysis of senile plaques, Sakae et al. observe the presence of aluminum in the plaques while no aluminum was found in the extracellular space or in the cytoplasm of the studied nerve cells (17). A review of multiple studies into aluminum's association with neurodegeneration relating to AD demonstrates aluminum is noted to be associated with the development of AD (18). Aluminum is shown to form structured aggregates with A $\beta$  and results in high neurotoxicity (19). Lead exposure results in increased A $\beta$  fibril formation and plaque deposition (20). Other work also shows exposure to lead results in amyloidogenic activity and AD-associated pathology (19). AD research has also shown a possible association between mercury and AD (21) where mercury exposure could increase the risk of developing AD (22). Cadmium interacts directly with A $\beta$  forming aggregates and is considered a possible risk factor in AD as well (23). Heavy and other metals are central to the AD pathology.

## Background and rationale

Despite substantial research, the precise mechanisms underlying AD remain elusive. Histological analysis of AD-affected brains reveals several cellular dysfunctions, many linked to A $\beta$ . While the prevailing hypothesis suggests that A $\beta$  contributes to neurodegeneration, recent findings indicate that A $\beta$  might play a protective role supporting our decade long proposal. This current article builds on our previous work (6) proposing that the upregulation of BACE1 and subsequent production of A $\beta$  are part of a cellular response to inflammation initiated by the oxidative heavy or other metal toxicity, a significant but often overlooked factor in sporadic AD as well (24).

## The hypothesis

Amyloid  $\beta$ -peptides and the  $\beta$ -secretase enzyme (BACE1) activity are part of an intentionally designed cellular defense mechanism against

### Amyloid $\beta$ 42

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

charged amino acid segment

### Amyloid $\beta$ 43

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIAT

### Amyloid $\beta$ 39

DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGV –VIAT

LVFFA - hydrophobic moiety

GAIIGLMVGGVVIA - hydrophobic moiety

S, Y, T - potential phosphorylation sites

FIGURE 1

Showcases the different domains of the BACE1-Generated ( $\beta$ -Secretase Enzyme) A $\beta$  peptide associated with metal ion chelation and those with hydrophobic activity known to facilitate aggregation and Beta sheet formation (46). In particular, the side-by-side histidine (13 and 14) residues formed bridges through metal cross-linking providing insight on another feature promoting the aggregation of A $\beta$  protein referred to in the medical community as 'pathogenic aggregation' (50), but considered by this paradigm to be an intended biological design to protect the brain from oxidation (including Fenton Reaction).

metal toxicity. This challenges the conventional understanding of the A $\beta$  peptide in the AD pathogenesis. It is not until this BACE1 system, primarily the associated amyloid plaque deposit sites, are saturated with heavy and other metals and the environmental exposure to these cations continues to influx oxidative ions into the brain, do the indications of neurodegeneration begin to become symptomatic.

## Evolution of the hypothesis

Contrary to the current AD model that considers BACE1 activity as aberrant, we suggest that increased BACE1 activity and subsequent A $\beta$  production are neuroprotective responses to heavy and other metal toxicity.

BACE1 activation is directly related to the escalation of NF- $\kappa$ B signaling – the inflammatory signaling pathway (14). As inflammatory signaling escalates BACE1 activity is triggered to escalate as well (13).

It is proposed that this incremental inflammatory activity is reflective of heavy or other metal toxicity and the incremental oxidative activity it promotes. Oxidation and inflammation go hand in hand; one facilitating the other in a cyclical fashion as we have proposed (24, 25).

This hypothesis posits that A $\beta$  peptides chelate and sequester free metals, forming extracellular amyloid plaques. These plaques can be made up of a variety of A $\beta$  peptide types or species reflecting the different peptides generated by differing processes and conditions, including mutations (PSEN) (25).

Additionally, A $\beta$  may cross cell membranes to chelate intracellular metals, subsequently exporting these complexes to the extracellular space for sequestration where the neuron can be protected from the oxidative effects (26).

Furthermore, it is suggested herein that this chelation and sequestration system can work for long periods in one's life to protect the brain from oxidative stress until the deposit sites- plaques – become too numerous and saturated with heavy or other metals. At this late stage in the disease evolution, the metal load begins to have a more deleterious effect on the brain resulting in intracellular TAU disruption and irreversible neuron damage leading to apoptosis.

The amyloid plaque is a healthy disposal site; while the TAU-specific anomalies or pathology (hyperphosphorylation and aggregation) are indicative of the progressed state of neurodegeneration (27). It is proposed that each of us has individual predispositions for tolerating such oxidative activity characterized by the rate and type (genetically influenced as well) of A $\beta$  peptide processing and the degree of functionality of endogenous antioxidant systems modulated by Nrf2 transcription which is responsible for catalase, glutathione peroxidase, heme-oxygenase and superoxide dismutase generation. Additionally, the level and duration of heavy metal exposure all play a role in producing a variable pathological risk for clinical symptom manifestation from one person to another.

TAU is a microtubule protein that stabilizes the microtubule to serve as a cytoskeleton anchoring organelles (28). The microtubule system also serves as the cell's 'railway system' for the movement or trafficking of materials within the cell (29). In the context of the proposed paradigm, as intolerance for heavy metal load progresses due to the multifactorial condition, oxidative activity can escalate to advance neuroinflammation, TAU protein hyperphosphorylation and subsequent microtubule disruption.

Continuing in the context of the proposed paradigm: At this advanced stage of the AD pathology when the microtubule system is interrupted by TAU hyperphosphorylation, the A $\beta$  protein is no longer translocated due to interruption of trafficking. It now accumulates intracellularly facilitating hyper-oxidative ROS levels and contributes to irreversible neuron apoptosis.

The pathology of Traumatic Brain Injury (TBI) also results in exposure to metal. Hemorrhage in and around the injured brain area results in iron deposition and a progressive neurodegenerative process as a result of the metal exposure (30). TBI is intimately associated with development of A $\beta$  plaques just like those found in Alzheimer's disease (29, 31). We proposed this as a factor of concern in our 2015 paper with more recent work expressed in the public domain today by Tang et al. demonstrating such. Historical research has shown that cellular distribution of iron in AD brains is also similar to that in TBI (32).

Neuroinflammation and iron aggregation are characteristic conditions of neurodegenerative diseases like AD, Parkinson's disease and common TBI (33). Ultimately it is shown that abnormal iron homeostasis induces hydroxyl radical production, and the elevated oxidation subsequently results in aberrant structure and function in the brain; and escalated inflammatory activity (34). Iron is detected with significance in post-mortem analysis of AD brains; and herein hemoglobin binds with the A $\beta$  peptide and localizes in the amyloid plaque as expected (35). Iron chelation to A $\beta$  also enhances neurotoxicity (36) of the A $\beta$  peptide likely because of the oxidative activity the complex bears before it is sequestered within the plaque. Amyloid plaques harbor iron, copper and zinc (37, 38).

## Hypothesis testing by way of meta-analysis

Compelling evidence supports this protective role of A $\beta$ . Studies show that as much as a third of older healthy adults show significant A $\beta$  plaque deposition in the brain (39). These deposits precede and are even considered independent of declines in cognitive deficits. Studies definitively show that heavy and other metals interact intimately with A $\beta$  peptide in various ways including in solution and in the cell membrane (40, 41). Heavy metals are implicated in AD pathology and AD-like disease pathologies. Even metals as ubiquitous as copper are shown to chelate the A $\beta$  peptide and when removed from the A $\beta$  peptide cause inhibition of A $\beta$  assembly (42) falling in perfect alignment with our proposed theory that positions A $\beta$  as a component of an intentionally designed protective chelation system.

Our 2015 published theory leads us to dive deeper today into the analysis of the amino acid sequence of the A $\beta$  peptide revealing some unique supportive features. The first half of the A $\beta$  peptide sequence, as seen in Figure 1, is designed for chelation. Independent research diving into the peptide's first 16 amino acids shows that this section alone of the peptide can bind up to four copper ions (II) (40). The A $\beta$  peptide is derived from the precursor protein, amyloid precursor protein (APP), as a function of two cleavages by two enzymes. The 42 and 43 amino acid A $\beta$  peptide, A $\beta$ 42 and A $\beta$ 43, are the more amyloidogenic and pathogenic peptides. These two, A $\beta$ 42 or A $\beta$ 43, polymerize rapidly and are highly associated with AD (43). If we look above in (44) Figure 1 at the BACE1-generated A $\beta$ 42, we see a 42 amino acid peptide (and others) each with unique features.

They each have a hydrophobic moiety expressed in bold (GAIIGLMVGGVVIA) that facilitates aggregation of peptides in aqueous solution. The tail end on the C-terminal end of the peptide has a long hydrophobic region where G (Glycine) is intermingled as the only hydrophilic inclusion (44, 45). We also have a segment of the peptide that boasts a charged amino acid section (DAEFRHDSGYEVHHQK), which also includes the two side-by-side histidine amino acids previously discussed in Figure 1 and highlighted mechanistically in Figure 2.

In fact, research by Faller and Hureau (45) has demonstrated a probability of copper, iron and even zinc co-ordination with the tail ends of the key amino acids in this hydrophobic segment while these ions have been shown to be intimately involved in the AD pathology (19, 46, 47, 49). This proposed theory showcases this amino acid-metal cross bridging (48) as a protective mechanism.

Showcases the different domains of the BACE1-Generated ( $\beta$ -Secretase Enzyme)  $A\beta$  peptide associated with metal ion chelation and those with hydrophobic activity known to facilitate aggregation and Beta sheet formation (46). In particular, the side-by-side histidine (13 and 14) residues formed bridges through metal cross-linking providing insight on another feature promoting the aggregation of  $A\beta$  protein referred to in the

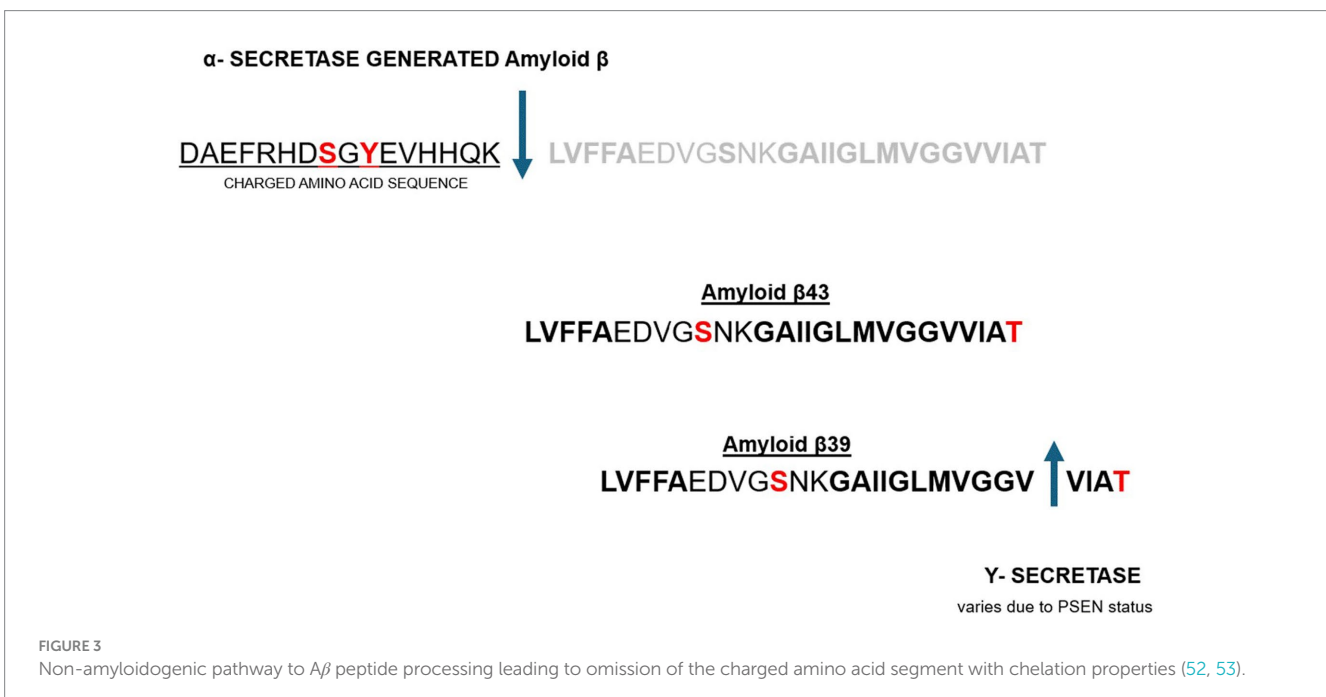
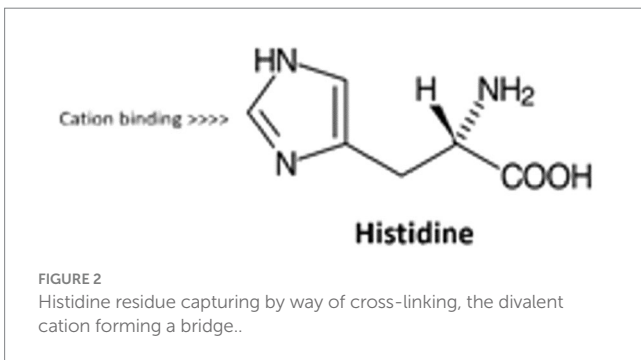
medical community as ‘pathogenic aggregation’ (50), but considered by this paradigm to be an intended biological design to protect the brain from oxidation (including Fenton Reaction).

### Histidine residue capturing by way of cross-linking, the divalent cation forming a bridge

Ultimately, there are two pathways that processing of the APP precursor protein can take to final  $A\beta$  peptide end product. One is the previously described BACE1 and the downstream  $\beta$ -Secretase cleavage as seen in Figure 1. This pathway results in an  $A\beta$  peptide that has irrefutable chelation potential as described above. This path is considered the amyloidogenic pathway and conducive to or associated with AD pathology (51). The other pathway is considered non-amyloidogenic and involves cleavage by  $\alpha$ -Secretase and is portrayed in Figure 3, below. This latter path yields an  $A\beta$  peptide that voids the charged amino acid segment and voids the histidine repeats that are intimately associated with metal chelation as portrayed in Figure 3.

Non-amyloidogenic pathway to  $A\beta$  peptide processing leading to omission of the charged amino acid segment with chelation properties (52, 53).

The proposed hypothesis underwriting the new paradigm suggests that BACE1 activation by the inflammatory response results in the downstream  $\beta$ -Secretase cleavage to produce the biological countermeasure (amyloidogenic peptide) to the excessive oxidation and inflammation. This amyloidogenic peptide is ultimately produced by intentional biological design in response to metal toxicity and the oxidative and inflammatory result of that uncontrolled oxidation. Alternatively, a peptide is produced in the absence of the oxidative and inflammatory activity where NF- $\kappa$ B Signaling would not be heightened. In this latter case  $\alpha$ -Secretase cleavage of the APP precursor peptide





would ensue. Typically, a 'normal brain' will have small levels of A $\beta$  protein. Both enzymes,  $\beta$ -Secretase and  $\alpha$ -Secretase compete in this 'normal' healthy brain but  $\beta$ -Secretase prevails as an APP cleavage enzyme if NF- $\kappa$ B Signaling is robustly active (12). As much as 80 percent of AD brains have elevated  $\beta$ -Secretase activity and low  $\alpha$ -Secretase activity (52). Researchers have concluded that this high  $\beta$ -Secretase and low  $\alpha$ -Secretase finding in the AD brain "may account for the means by which the majority of people develop AD" (54, 57).

However, in the context of our paradigm shift the proposed hypothesis positions this a little differently: The heavy and other metal toxicity is the cause of the high  $\beta$ -Secretase activity and low  $\alpha$ -Secretase activity dynamic. The resulting A $\beta$  peptide (with charged amino acids) with chelated metals which aggregate as plaque development is the consequential attempt by the body to protect itself.

Looking beyond the peptide and at the plaque, we see studies indicate that A $\beta$  peptide aggregation and plaque formation precede Alzheimer's symptoms (53–55), suggesting a long-term protective mechanism against metal-induced oxidative damage. This falls in line with our theory. Research by Rogers et al. showcases their discovery of an Iron-Responsive Element (IRE) built into the APP transcript. Further evidence that APP is, in fact, a metalloprotein and this too supports the current hypothesis that metals modulate APP regulation (56). Ashok et al. demonstrate that environmental pollutants can contribute AD pathology – an increase in A $\beta$  in the rat brain and ensuing cognitive deficits as a function of exposure to environmental As, Cd and Pb (57).

Other enzymes involved in A $\beta$  peptide processing include  $\gamma$ -Secretase. Although we have not assigned much attention to  $\gamma$ -Secretase in this paper, it has garnered lots of attention by researchers historically because it is the enzyme that cleaves the A $\beta$  peptide so it can be released. It shortens the A $\beta$  peptide as seen in Figure 3 into what is said to be shorter, 'stickier' peptides (58, 59). Other causes of the AD pathology include various mutations that lead to Familial Alzheimer's Disease (FAD) characterized by early development of A $\beta$  peptide and plaques (58, 59) and the toxicity from these plaques and migrating A $\beta$  peptides may also be associated with the metals that these peptides are spontaneously chelating.

## Implications for AD progression

The proposed paradigm states that neurons can tolerate metal toxicity in the early stages of exposure due to BACE1-mediated A $\beta$  peptide production. However, as AD progresses and heavy metal exposure persists, uncontrolled metal accumulation and reactive oxygen species (ROS) levels overwhelm this protective mechanism. This leads to increased inflammation, Tau protein hyperphosphorylation, and disruption of microtubule stability, eventually causing neuron apoptosis, tissue loss and an exponential advancement of disease.

## Conclusion

This article presents a paradigm shift in our understanding of A $\beta$ -peptides in AD. Rather than being solely pathogenic, A $\beta$  and

BACE1 activity may represent strategic cellular defenses against metal toxicity. These findings highlight the need for a reassessment of therapeutic strategies targeting A $\beta$  production, suggesting that inhibition of BACE1 may inadvertently disrupt protective mechanisms and exacerbate disease progression.

This model indicates that the current AD treatment approach of inhibiting BACE1 may not support resolution of disease progression and may, in fact, result in exacerbation. While typical AD treatment protocols also include the application of anti-inflammatory strategies which may mitigate progression of symptoms for a short period, failure to terminate exposure to the environmental sources of oxidative heavy metals will continue to strain the biological system beyond the anti-inflammatory countermeasure especially in the context of BACE1 inhibition.

## Future directions

It is estimated that 5.5 million North Americans suffer from varying degrees of Alzheimer's disease (AD) and by the year 2050 it may be one in 85 people globally (100 Million). While we believe that metal toxicity plays a significant role in sporadic Alzheimer's disease, the current literature speaks to the mere involvement of metal ions. Studies and reviewers have yet to link cellular events including known structural changes such as amyloid plaque development to this metal toxicity the way it was originally proposed by us in 2015 and further elaborated here.

Further research is necessary to validate these findings and explore the therapeutic potential of modulating heavy metal toxicity by chelation therapies and by this treatment modality positively affecting A $\beta$  production and BACE1 activity. Understanding the dual roles of A $\beta$  in neuroprotection and neurodegeneration and the central causal role that metal toxicity may be playing could lead to more nuanced and effective treatments for AD.

Research will need to consider how the administration of exogenous ketone body,  $\beta$ -hydroxybutyrate (3-hydroxybutyrate), might sustain neurons as an ATP substrate alternative to glucose while in the advanced state of AD and the type III diabetic condition. AD and type III diabetes share mechanisms that result in co-manifestation (60). These ketone bodies are ATP substrates and do not depend on insulin signaling for uptake, but they are also anti-inflammatory agents that cross the blood brain barrier to serve the type III diabetic brain in many ways (61).

This ketone body administration might support neurons to the point where apoptosis and loss of brain mass is slowed down; while the metal exposure is identified and eliminated. Alternatively, facilitation of endogenous ketone production via the ketogenic diet or the use of other facilitators of ketogenesis such as caprylate or derivatives thereof now in research. However, researchers will need to investigate how robust diagnostic programs can be applied to identify heavy metal toxicity in the brains of AD patients and develop chelation therapy that can effectively remove heavy metal toxicity without disrupting extracellular amyloid plaque sequestration of these metals before too much irreversible damage is done (62, 63). This preventive and interceptive strategy might be the best way to circumvent the progression of AD to dysfunctional states of disease.

## Author contributions

FC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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pharmacology of nutritional, nutraceutical and pharmaceutical agents. This current article is simply a function of interest and curiosity and did not utilize funds to execute experimental activity.

## Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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