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A disease-modifying treatment for Alzheimer's disease: focus on the trans-sulfuration pathway

https://doi.org/10.1515/revneuro-2019-0076
Received August 9, 2019; accepted August 31, 2019; previously published online November 21, 2019

Abstract: High homocysteine levels in Alzheimer's disease (AD) result from low activity of the trans-sulfuration pathway. Glutathione levels are also low in AD. L-cysteine is required for the synthesis of glutathione. The synthesis of coenzyme A (CoA) requires L-cysteine, which is synthesized via the trans-sulfuration pathway. CoA is required for the synthesis of acetylcholine and appropriate cholinergic neurotransmission. L-cysteine is required for the synthesis of molybdenum-containing proteins. Sulfite oxidase (SUOX), which is a molybdenum-containing protein, could be dysregulated in AD. SUOX detoxifies the sulfites. Glutaminergic neurotransmission could be dysregulated in AD due to low levels of SUOX and high levels of sulfites. L-cysteine provides sulfur for iron-sulfur clusters. Oxidative phosphorylation (OXPHOS) is heavily dependent on iron-sulfur proteins. The decrease in OXPHOS seen in AD could be due to dysregulations of the trans-sulfuration pathway. There is a decrease in aconitase 1 (ACO1) in AD. ACO1 is an iron-sulfur enzyme in the citric acid cycle that upon loss of an iron-sulfur cluster converts to iron regulatory protein 1 (IRP1). With the dysregulation of iron-sulfur cluster formation ACO1 will convert to IRP1 which will decrease the 2-oxglutarate synthesis dysregulating the citric acid cycle and also dysregulating iron metabolism. Selenomethionine is also metabolized by the trans-sulfuration pathway. With the low activity of the trans-sulfuration pathway in AD selenoproteins will be dysregulated in AD. Dysregulation of selenoproteins could lead to oxidant stress in AD. In this article, we propose a novel treatment for AD that addresses dysregulations resulting from low activity of the trans-sulfuration pathway and low L-cysteine.

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Keywords: Alzheimer's disease (AD); amyloid beta; cystathionine beta-synthase (CBS); homocysteine; trans-sulfuration pathway.

Introduction

In 2013, the US official death certificates recorded 84 767 deaths from Alzheimer's disease (AD) making it the sixth leading cause of death (Alzheimer's Association, 2016). In one longitudinal population-based study of 10 802 participants, it was reported that in 2010, there were approximately 600 000 deaths of individuals with AD comprising 32% of the deaths of the older population (Weuve et al., 2014). In 2010, the projected costs of AD and other dementias were estimated to be $172 billion (Alzheimer's Association, 2010). The total payment for healthcare services for people aged ≥65 years with dementia in 2016 was estimated at $236 billion (Alzheimer's Association, 2016). Further, the burden on families with individuals with AD is tremendous.

Homocysteine can be metabolized via the remethylation of homocysteine to L-methionine by methionine synthase (Moustafa et al., 2014). They can also be metabolized via the trans-sulfuration pathway which synthesizes L-cysteine. This paper proposes that high homocysteine levels in AD are due to the low activity of the trans-sulfuration pathway. Patients with AD have high homocysteine levels. The total serum homocysteine levels are increased in AD compared to controls (Joosten et al., 1997; Clarke et al., 1998; McCaddon et al., 1998). The plasma total homocysteine levels are increased in AD compared to controls (Seshadri et al., 2002; Gallucci et al., 2004; Ma et al., 2017). The severity is positively related to serum homocysteine levels (McCaddon et al., 2001) and the increase in plasma homocysteine levels are positively related to the disease severity (Kitzlerová et al., 2014; Farina et al., 2017). The elevated plasma homocysteine levels (Seshadri et al., 2002; Ravaglia et al., 2005; Annerbo et al., 2009), and the elevated serumhomocysteine levels can predict the development of AD (Zylberstein et al., 2011).

Disease-modifying treatments for AD can change the pathological steps that lead to AD (Galimberti and Scarpini,

2011). There are currently no disease-modifying treatments for AD (Cummings et al., 2018). In terms of developing drugs for AD, the failure rate is 99.6% (Cummings et al., 2014). The few medications available for AD only modestly affect symptoms and do not modify disease progression (Di Santo et al., 2013). There is an urgent need for the development of disease-modifying therapies for AD (Suzuki et al., 2017). By addressing the dysregulation of the trans-sulfuration pathway and dysregulations of pathways downstream from L-cysteine synthesis in AD, the biological dysregulations that are at the headwaters of the biological dysregulations can be modified.

We propose a treatment for AD, which targets a low activity of the trans-sulfuration pathway and low activity of pathways downstream from L-cysteine synthesis that can be disease-modifying in AD (see Table 1). The proposed treatment (a) increases the levels of molybdenum-containing proteins through supplementation with sodium molybdate, (b) increases the levels of selenoproteins through supplementation with Se-methylselenocysteine, (c) increases the activity of enzymes in the trans-sulfuration pathway through supplementation with taurine, L-arginine, and L-citrulline, (d) supports iron-sulfur proteins such as aconitase 1 (ACO1) and iron-sulfur proteins involved in oxidative phosphorylation (OXPHOS) through supplementation with heme iron polypeptide, coenzyme Q10, and eicosapentaenoic acid, (e) supports copper proteins through supplementation with copper, (f) supports increased protein synthesis through supplementation with whey protein and, (g) supports enzymes involved in L-cysteine metabolism and selenium metabolism through supplementation with vitamin B6.

Further evidence that the trans-sulfuration pathway is dysregulated in Alzheimer's disease

L-cysteine is synthesized by way of the trans-sulfuration pathway (Figure 1). L-cysteine is the rate-limiting amino acid in the synthesis of glutathione, which is a tri-peptide

Table 1: Supplements that can be used to treat Alzheimer's disease (AD).

Treatment	Actions	Symptoms targeted
Sodium molybdate	Increases sulfite oxidase levels thereby decreasing sulfite levels	Enhances memory and learning by addressing glutaminergic dysregulations
Se-methylselenocysteine	Increases levels of selenoproteins	Decreases purposeless behaviors such as apathetic behavior, wandering, and aberrant motor activities
Iron from heme iron polypeptide	Increases activity of aconitase 1 (ACO1) which supports the citric acid cycle, decreases activity of iron regulatory protein 1, and increases iron-sulfur cluster formation whereby oxidative phosphorylation (OXPHOS) is supported	Improves executive function and alleviates depression by addressing deficits in OXPHOS
Copper from copper gluconate	Supports iron transport and addresses copper deficiencies whereby OXPHOS is supported	Improves executive function and alleviates depression by addressing deficits in OXPHOS
Taurine	Increases activity of enzymes in the trans-sulfuration pathway, increases hydrogen sulfide levels, and decreases homocysteine levels	Increases activity of enzymes in the trans-sulfuration pathway supporting activities of other supplements
1:1 Combination of L-arginine/L-citrulline	Increases expression of cystathionine gamma-lyase (CTH)	Increases activity of CTH supporting activities of other supplements
Coenzyme Q10	Supports oxidative phosphorylation	Improves executive function and alleviates depression by addressing deficits in OXPHOS
Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) where EPA levels are 60% or greater	Supports mitochondrial beta-oxidation and oxidative phosphorylation	Improves executive function and alleviates depression by addressing deficits in OXPHOS
Whey protein	Increases levels of 2-oxoglutarate and glutathione, and supports increased protein synthesis	Alleviates fatigue and irritability
Vitamin B6	Supports enzymes involved in L-cysteine metabolism and selenium metabolism	Supports vitamin B6 dependent enzymes in the trans-sulfuration pathway supporting activities of other supplements

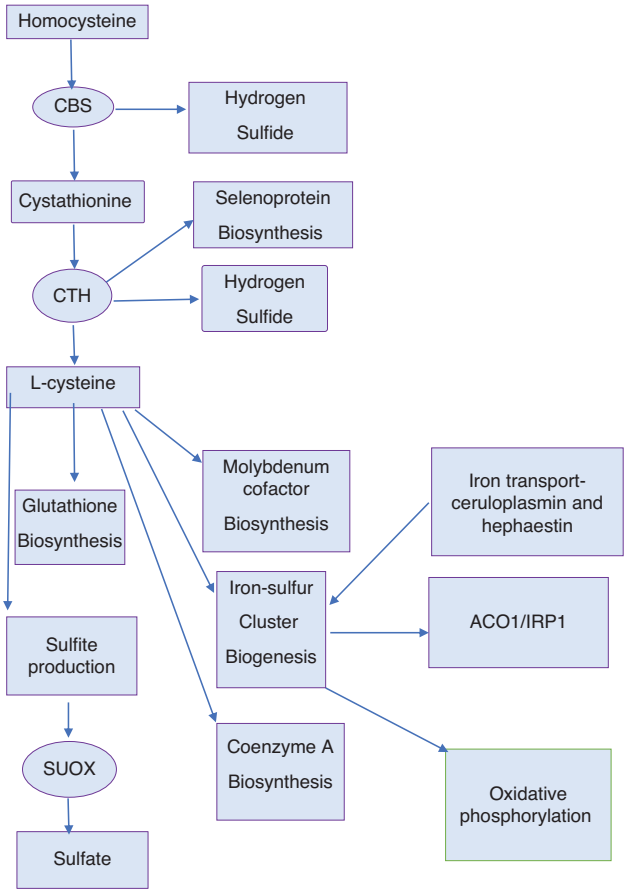

Figure 1: The trans-sulfuration pathway (cystathionine beta-synthase and cystathionine gamma-lyase) and downstream pathways.
Arrows point to downstream metabolites and downstream pathways. In Alzheimer's disease (AD) decreased activity of the trans-sulfuration pathway and decreased levels of cysteine lead to low levels of hydrogen sulfide, decreased selenoprotein synthesis, decreased synthesis of the molybdenum cofactor, decreased iron-sulfur cluster formation, decreased levels of coenzyme A, decreased oxidative phosphorylation, and decreased iron transport by ceruloplasmin and hephaestin all of which contribute to the development of AD.

composed of L-cysteine, glutamate, and glycine (Lu, 2013). Plasma glutathione levels are decreased in AD compared to controls (Calabrese et al., 2006; Bermejo et al., 2008; Rani et al., 2017). Glutathione levels as measured by *in vivo* proton magnetic resonance spectroscopy were lower in hippocampi and frontal cortices of patients with AD compared to healthy controls where decreases in glutathione were correlated to declines in the cognitive function (Mandal et al., 2015). Hydrogen sulfide (H_2S) is synthesized by cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CTH) which are the two enzymes in the trans-sulfuration pathway (Kimura, 2011). In postmortem brains of individuals who had AD, the H_2S levels were severely reduced compared to the controls while homocysteine levels were high compared to controls which indicates that CBS, which synthesizes H_2S and metabolizes homocysteine, could be dysregulated in AD (Eto et al., 2002). In plasma of individuals with AD H_2S levels are low and homocysteine levels are high compared to controls with H_2S levels negatively correlated to disease severity and homocysteine levels positively correlated disease severity (Liu et al., 2008). In animal models studies, the administration of H_2S is protective against the development of AD (Xuan et al., 2012; Giuliani et al., 2013; Kamat et al., 2016).

Selenomethionine, which is the predominant food form of selenium, is metabolized by the trans-sulfuration pathway (Burk and Hill, 2015). CTH contributes to cytosolic glutathione peroxidase (GPX) synthesis in the liver (Okuno et al., 2006). The activity of the trans-sulfuration pathway is low in AD whereby L-selenomethionine is an ineffective source of selenium for selenoprotein synthesis in AD, which would lead to low selenoprotein levels in AD. GPX1, GPX2, GPX3, GPX4, and GPX6 are selenoproteins which neutralize hydrogen peroxide (Brigelius-Flohé and Maiorino, 2013). Research shows that GPX activity is decreased in AD. In patients with AD erythrocyte GPX is decreased compared to controls (Jeandel et al., 1989; Vural et al., 2010). In patients with AD the serum GPX levels are low compared to controls (Padurariu et al., 2010). Plasma GPX is low in patients with AD compared to controls (Rinaldi et al., 2003). Not all research in AD shows GPX activity as being decreased in AD. Iodothyronine deiodinase I, iodothyronine deiodinase 2, and iodothyronine deiodinase 3 are selenoproteins involved in thyroid function (Köhrle, 1999). Deiodinase 2 activates 3,3′,5-triiodothyronine (T_3) by converting the prohormone, thyroxine (T_4), to T_3 by outer ring deiodination with T_3 being much more active than T_4 (Bianco and Kim, 2006). Decreases in levels of iodothyronine deiodinases in AD could lead to decreases in T_3 in AD. Research shows free T_3 levels are low in AD compared to controls (Thomas et al., 1987; Quinlan et al., 2019). Serum T_3 levels are low in AD compared to controls (Karimi et al., 2011). Low serum-free T_3 levels increase the risk of developing AD (Quinlan et al., 2019). As is the case with GPX not all research in AD shows T_3 levels as low in AD. As will be explained below, AD can be associated with epigenetic changes whereby some variability in test findings would be expected. Methionine sulfoxide reductase B1, which reduces methionine sulfoxides to methionine decreasing oxidant stress, is a selenoprotein readily regulated by selenium (Novoselov et al., 2010). Methionine sulfoxide reductase B1 levels in neutrophils are reduced in

AD compared to controls (Achilli et al., 2018). Decreases in methionine sulfoxide reductase B1 in AD could be due to an inability to metabolize selenomethionine in AD so that selenomethionine can be used for selenoprotein synthesis. Selenium levels in plasma, erythrocytes, and nails are significantly decreased in AD compared to controls (Cardoso et al., 2010). Decreased selenium levels in AD could be due to an inability to metabolize food forms of selenium in AD. Decreased plasma selenium levels are a risk factor for cognitive decline (Akbaraly et al., 2007; Berr et al., 2012). Decreased selenium levels as tested by nail clippings are a risk factor for cognitive decline (Gao et al., 2007). Selenium levels are inversely associated with homocysteine levels in elderly humans (González et al., 2004).

Research points to selenium and selenoproteins as being protective against the development of AD (Du et al., 2016a,b). In animal models of AD, Se-methylselenocysteine ameliorates neuropathological and cognitive deficits by decreasing amyloid-β (Aβ) generation by inhibiting the expression of the amyloid precursor protein (APP) and beta-secretase, and decreases tau hyperphosphorylation and neurofibrillary tangles (Xie et al., 2018). The ability of Aβ to form plaques is central to AD pathology (Walsh and Teplow, 2012). Gamma-secretase along with beta-secretase cleaves APP to form Aβ (Chow et al., 2010). Sodium selenite inhibits gamma-secretase (Tung et al., 2008). Selenoprotein P and selenoprotein M block Aβ42 aggregation and toxicity (Du et al., 2013). Tau proteins are hyperphosphorylated in AD (Iqbal et al., 2010). Sodium selenate lessens tau hyperphosphorylation pathologies in animal models of AD (van Eersel et al., 2010). Selenoprotein S reduces phosphorylation of tau (Rueli et al., 2017). Ebselen, a lipid-soluble selenium compound, ameliorates amyloid beta pathology, tau pathology, and cognitive impairment in animal models of AD (Xie et al., 2017).

Synthesis of acetylcholine requires CoA (Jope and Jenden, 1980). CoA is synthesized from pantothenic acid and L-cysteine (Leonardi and Jackowski, 2007). A key factor in the survival of cholinergic neurons in neurodegenerative diseases is the availability of acetyl-CoA (Szutowicz et al., 2013, 2014). With the trans-sulfuration pathway dysregulated in AD there will be a decrease in the synthesis of L-cysteine which will lead to decrease in the synthesis of CoA which will in turn lead to decrease in acetyl-CoA synthesis adversely affecting cholinergic neurons in AD. Treatments that address cholinergic neurotransmission dysregulations could have a positive effect on symptoms of AD (Ferreira-Vieira et al., 2016). Enhancing CoA synthesis in AD could increase acetylcholine synthesis and thereby ameliorate symptoms of AD.

Sulfites and Alzheimer's disease

Xanthine oxidase (XO) is a molybdenum-containing protein (Ryan et al., 1995). Uric acid is synthesized by XO (Maiuolo et al., 2016). Inhibitors of XO, such as allopurinol, are used to lower uric acid levels in the treatment of gout (Ojha et al., 2017). A meta-analysis of uric acid levels in AD which covered 24 studies shows that there is an inverse association between serum uric acid levels and AD with high serum uric acid levels significantly associated with decreased risk of AD (risk ratio = 0.66, 95% CI 0.52–0.85, $p = 0.001$) (Du et al., 2016a,b). Uric acid levels are inversely associated with tauopathies in AD (Schirinzi et al., 2017). High uric levels are associated with increased risks of developing cardiovascular disease (Doehner and Landmesser, 2011). Xanthine oxidase generates hydrogen peroxide (Kelley et al., 2010). With appropriate selenium supplementation to increase GPX, which neutralizes hydrogen peroxide, there could be no association between uric acid levels and cardiovascular disease. This paper proposes that uric acid levels are low in AD due to decreases in the synthesis of L-cysteine which is required for synthesis of the molybdenum co-factor (MoCo).

MoCo consists of molybdenum bound to molybdopterin (Mendel, 2015). Cysteine desulfurase by transferring sulfur from L-cysteine to molybdenum cofactor synthesis 3 (MOCS3) provides sulfur required for MoCo biosynthesis in humans (Marelja et al., 2008, 2013). The gene for cysteine desulfurase and the gene for MOCS3 are not associated with AD (Bertram et al., 2007 – AlzGene database, URL: www.alzgene.org). Sulfites from L-cysteine and L-methionine metabolism must be detoxified which is done by SUOX (MacLeod et al., 1961). SUOX is a molybdenum-containing protein (Kappler and Enemark, 2015). SUOX deficiency due to mutations in genes for SUOX or mutations in genes coding for MoCo is a lethal disease causing severe neurological impairment for which there is no effective treatment (Karakas et al, 2005). The gene for SUOX is not associated with AD (Bertram et al., 2007 – AlzGene database, URL: www.alzgene.org). No mutations in genes required for SUOX or MoCo synthesis are being proposed in AD by this paper.

What is being proposed in this paper is that in AD at the stage where cysteine desulfurase transfers sulfur from L-cysteine to MOCS3, due to shortages of L-cysteine, that MOCS3 does not obtain the needed sulfur whereby there will be low levels of MoCo which will lead to low levels of molybdenum-containing proteins, such as XO and SUOX, in AD. Dysregulation of the trans-sulfuration pathway in AD dysregulates SUOX which leads to high levels of sulfites in AD with attendant neurological toxicities.

Sulfites adversely affect glutamatergic neurotransmission and inhibit glutathione metabolism related enzymes in the cortex whereby babies born with mutated SUOX genes are neurologically severely impaired (Parmeggiani et al., 2015). Glutamate dehydrogenase is inhibited by sulfites which leads to decreases in the synthesis of 2-oxoglutarate by glutamate dehydrogenase (Zhang et al., 2004). NMDA receptors are adversely affected by sulfites as sulfites degrade the NR2A and NR2B subunits of the NMDA receptor (Oztürk et al., 2006). Dysregulation of glutamatergic neurotransmission is hypothesized as being a key factor in the development of AD (Butterfield and Pocernich, 2003).

In AD high levels of sulfites resulting from decreases in SUOX stemming from decreases in L-cysteine synthesis could lead to dysregulation of glutamatergic neurotransmission, severe neurological impairments, and impaired learning and memory. Appropriate glutaminergic neurotransmission is required for learning and memory (Riedel et al., 2003; Niciu et al., 2012). Long-term potentiation, which is required for memory formation, is associated with glutamate NMDA receptors (Malenka and Bear, 2004) which are dysregulated by sulfites (Oztürk et al., 2006). Long-term potentiation is tied to long-lasting increases in synaptic strengths whereby dysregulation of long-term potentiation could disrupt long-term memory. Research indicates that NMDA receptor hypofunction can lead to neurodegeneration and cognitive deterioration (Newcomer et al., 2000). NMDA receptors are present in the hippocampus which is involved in memory formation (Kumar and Foster, 2019). NMDA receptors in the hippocampus and amygdala are involved in learning and memory (Castellano et al., 2001).

Aconitase 1/iron regulatory protein 1 in Alzheimer's disease

Iron-sulfur clusters obtain sulfur from L-cysteine via cysteine desulfurase (Li et al., 2006). ACO1 is an iron-sulfur protein located in the cytoplasm (Klausner and Rouault, 1993). ACO1 is an enzyme in the citric acid cycle. ACO1 is a focus as ACO1 interconverts iron regulatory protein 1 (IRP1) (Rouault, 2006). IRP1 binds to iron responsive binding elements of mRNA involved in iron metabolism affecting the stability of mRNA transcripts (Sanchez et al., 2011). To act as an aconitase ACO1 must have a 4F-4S iron-sulfur cluster. Lacking a 4F-4S cluster ACO1 converts to IRP1 (Rouault, 2006). Disruption of iron-sulfur cluster formation activates IRP1 (Tong and Rouault, 2006). What is being proposed is that with decreases in the synthesis of L-cysteine in AD due to the low activity of the trans-sulfuration pathway the iron-sulfur cluster formation is decreased in AD whereby aconitase activity is decreased and IRP1 levels are increased which in turn dysregulates proteins regulated by IRP1. ACO1 is inactivated by hydrogen peroxide (Pantopoulos and Hentze, 1995). In AD with low activity of GPX the hydrogen peroxide levels will be high whereby ACO1 will be inactivated.

Levels of ACO1 and levels of APP in peripheral blood mononuclear cells in AD are lower than in controls (Guerreiro et al., 2015). This paper proposes that with iron-sulfur cluster formation dysregulated in AD due to low levels of L-cysteine ACO1 will convert to IRP1 whereby the ACO1 levels will be low in AD which is seen in AD. Aconitase 2 (ACO2) mRNA has an iron response element in the 5′ untranslated region which when bound by IRP1 represses translation of ACO2 mRNA (Kim et al., 1996). ACO2 levels are significantly lower in blood lymphocytes of individuals with AD compared to controls (Mangialasche et al., 2015). In AD high levels of IRP1, due to dysregulation of iron-sulfur cluster formation stemming from dysregulations of the trans-sulfuration pathway, could be lowering levels of ACO2.

mRNA transcripts for APP contain an iron response element in the 5′ untranslated region (Rogers et al., 2002). IRP1 destabilizes mRNA levels of APP whereby APP levels are increased by iron influx as iron influx decreases the levels of IRP1 (Cho et al., 2010). Although there are high levels of Aβ in AD, which is a cleavage product of APP, the levels of APP are low (Barger et al., 2008). With L-cysteine levels decreased in AD due to dysregulation of the trans-sulfuration pathway IRP1 levels will be high, APP levels will be low, ACO1 levels will be low and ACO2 levels will be low all of which fit available research findings.

In AD, there are significant decreases of ferroportin in peripheral blood mononuclear cells of patients with AD (Crespo et al., 2014). Ferroportin is reduced in postmortem brains in AD (Raha et al., 2013). Ferroportin mRNA possesses an iron response element in the 5′ untranslated region whereby IRP1 destabilizes mRNA of ferroportin (Liu et al., 2002). Ferroportin is the only known iron exporter (Ward and Kaplan, 2012). APP is involved in the stabilization of ferroportin with APP required for iron export (Wong et al., 2014). We here argue that dysregulation of the trans-sulfuration pathway in AD can disrupt iron-sulfur cluster formation which can increase IRP1 levels which decreases iron export by ferroportin. In AD, there are difficulties with iron stemming from the iron not being exported by ferroportin from cells. Iron chelators,

however, would not be an effective treatment for AD as iron chelators would increase levels of IRP1, decrease expression of ferroportin, and decrease the stability of ferroportin on cells membranes. Peripheral serum iron levels are low in AD compared to controls (Crespo et al., 2014; Kweon et al., 2019) which fits with IRP1 levels being high in AD and iron export from cells in AD being impaired.

IRP1 destabilizes mRNA transcripts of hypoxia inducible factor 2α (HIF2α) (Anderson et al., 2013). HIF2α induces adenosine triphosphate (ATP)7A, which is a copper transporter (Xie and Collins, 2011). Basal expression of high affinity copper uptake protein 1 is regulated by HIF2α (Pourvali et al., 2012). With high levels of IRP1 in AD mRNA of HIF2α will be destabilized whereby induction of copper transporters in AD by HIF2α will be reduced leading to copper deficiencies in AD. In AD there are low plasma copper levels compared to controls where copper levels are negatively correlated to severity of AD (Pajonk et al., 2005). There are greatly reduced copper levels in postmortem brains of AD patients (Xu et al., 2017). Copper bound to ceruloplasmin and hephaestin are ferroxidases which assist with iron transport (Frazer and Anderson, 2014). In AD there is decreased expression in peripheral blood mononuclear cells of ceruloplasmin mRNA compared to controls (Guerreiro et al., 2015). Levels of ceruloplasmin are low in AD postmortem brains compared to controls (Conner et al., 1993). Oxidative activity of ceruloplasmin in plasma of AD patients is greatly reduced as compared to controls (Snaedal et al., 1998). Ceruloplasmin and hephaestinare coordinated with ferroportin in export of iron from cells (Ward and Kaplan, 2012). HIF2α induces ferroportin transcription (Taylor et al., 2011). HIF2α also induces transcription of CBS (Takano et al., 2014). Decreases in HIF2α in AD due to high levels of IRP1 would lead to decreases in CBS, which metabolizes homocysteine, and increases homocysteine levels.

This research indicates that oxidant stress plays a large role in Aβ plaque formation (Gwon et al., 2012; Tamagno et al., 2012; Arimon et al., 2015). Low levels of selenoproteins, decreased iron export from cells by ferroportin and low levels of copper and copper ferroxidases which are needed for iron export would generate oxidant stress in individuals with AD which could lead to Aβ plaque formation.

Oxidative phosphorylation in Alzheimer's disease

Oxidative phosphorylation is highly dependent on proteins with iron-sulfur clusters. Nicotinamide adenine dinucleotide (NADH) dehydrogenase, succinate dehydrogenase, ubiquinol-cytochrome c reductase, and electron transfer flavoprotein dehydrogenase are enzyme complexes in the OXPHOS pathway with iron-sulfur clusters. NADH dehydrogenase contains up to 10 proteins with iron-sulfur clusters depending on species (Gnandt et al., 2016). Succinate dehydrogenase contains three iron-sulfur clusters (Johnson et al., 1985). Ubiquinol-cytochrome c reductase contains iron-sulfur clusters (Iwata et al., 1998). Electron transfer flavoprotein dehydrogenase contains a 4Fe-4S iron-sulfur cluster (Watmough and Frerman, 2010).

The iron-sulfur NADH ubiquinone oxidoreductase 24- and 75-kDa subunits of complex I of the OXPHOS pathway are significantly decreased in postmortem brains of individuals who had AD compared to controls with the 24-kDa subunit significantly reduced in temporal and occipital cortices while the 75-kDa subunit are significantly decreased in the parietal cortex in compared to controls (Kim et al., 2001). Research shows that in early AD and definite AD postmortem brain specimens that there is a downregulation mitochondrial genes in complex I of OXPHOS with the downregulation highest for the 15-kDA subunit of complex I, which is an iron-sulfur protein compared to controls (Manczak et al., 2004). There is also reduced expression of nuclear-encoded OXPHOS genes in blood in AD (Lunnon et al., 2017). There is a downregulation of expression for mitochondrial and nuclear genes coding for subunits of OXPHOS enzymes in AD (Chandrasekaran et al., 1996). Cytochrome c oxidase is reduced in platelets in AD compared to controls (Parker et al., 1990; Cardoso et al., 2004). Copper is required for cytochrome *c* oxidase (Horn and Barrientos, 2008). Decreased activity of OXPHOS in AD could be due to difficulties in synthesizing iron-sulfur clusters for iron-sulfur proteins in the OXPHOS pathway and also due to copper deficiencies leading to decreases in activity of cytochrome c oxidase.

How Alzheimer's disease differentiates from other illnesses where there are high homocysteine levels

Various neurological disorders besides AD are associated with high levels of homocysteine (Moustafa et al., 2015). Cerebrovascular, cardiovascular, and peripheral vascular diseases are associated with high levels of homocysteine (McKinley, 2000). High homocysteine levels are present in schizophrenia and increase as schizophrenia progresses

(Moustafa et al.,2014). Parkinson's disease is associated with high levels of homocysteine (Licking et al., 2017). Increased levels of homocysteine are associated with autism (Ali et al., 2011). Mania and euthymia in bipolar disorder are associated with increased levels of homocysteine (Salagre et al., 2017). A range of illnesses associated with high homocysteine levels and dysregulation of the trans-sulfuration pathway can develop due to different epigenetic changes in different illnesses. Dysregulation of the trans-sulfuration pathway with attendant high homocysteine levels could result in different illnesses in individuals due to different epigenetic changes that can result from dysregulations of ten-eleven translocation (TET) enzymes and JumonjiC-domain containing enzymes due to a lack of 2-oxoglutarate and oxidant stress resulting from dysregulations of selenoproteins.

Ten-eleven translocation enzymes are α-ketoglutarate and Fe (II) dependent enzymes which demethylate DNA (Rasmussen and Helin, 2016). JumonjiC-domain containing enzymes are α-ketoglutarate and Fe (II) dependent enzymes which demethylate lysine residues of histones (Tsukada et al., 2006; Hou and Yu, 2010). Activity of TET enzymes (Laukka et al., 2016; Bochtler et al., 2017) and the activity of JumonjiC-domain containing histone demethylases (Tarhonskaya et al., 2017) are regulated by levels of 2-oxoglutarate and levels of tricarboxylic intermediates. ACO1 and ACO2 are iron-sulfur enzymes in the first half of the citric acid cycle. Activity of ACO1 (Guerreiro et al., 2015) and activity of ACO2 (Mangialasche et al., 2015) are low in AD. ACO1 and ACO2 are needed to produce 2-oxoglutarate by the citric acid cycle. In the citric acid cycle 2-oxoglutarate is metabolized by the 2-oxglutarate dehydrogenase complex. In AD activity of the 2-oxglutarate dehydrogenase complex is decreased (Mastrogiacoma et al., 1996) which could be due to lack of the substrate, 2-oxoglutarate. Isocitrate dehydrogenase and alpha-ketoglutarate dehydrogenase are enzymes in the citric acid cycle after aconitase. In postmortem brains of individuals who had AD isocitrate dehydrogenase was decreased by 27% and the alpha-ketoglutarate dehydrogenase complex was decreased by –57% (Bubber et al., 2005).

The view being proposed is that in AD with decreases in activity of ACO1 and ACO2 and decreases in activity of isocitrate dehydrogenase there will be decreases in the synthesis of 2-oxglutarate by which there can be deficits in energy metabolism but where there will also be decreases in activity of DNA demethylating TET enzymes and histone demethylating JumonjiC-domain containing enzymes. In AD epigenetic dysregulations could arise from dysregulations of TET enzymes and JumonjiC-domain containing enzymes due to the lack of 2-oxogultarate. With high levels of sulfites glutamate dehydrogenase is inhibited which will decrease 2-oxoglutarate synthesis by glutamate dehydrogenase (Zhang et al., 2004) which will also decrease activity of TET enzymes and JumonjiC-domain-containing histone demethylases in AD resulting in epigenetic dysregulations.

Selenium has a range of epigenetic effects (Speckmann and Grune, 2015; Jabłońska and Reszka, 2017). In AD dysregulation selenoprotein synthesis due to dysregulation of the trans-sulfuration pathway could result in epigenetic changes resulting from oxidant stress. Hydrogen peroxide is neutralized by GPX enzymes, with GPX1, GPX2, GPX3, GPX4, and GPX6 being selenoproteins (Brigelius-Flohé and Maiorino, 2013). TET enzymes and Jumonji C-domain-containing histone demethylases are inhibited by hydrogen peroxide (Niu et al., 2015). In AD DNA demethylation processes and histone demethylation processes could be dysregulated by decreases in selenoproteins which would give rise to epigenetic changes in AD.

A proposed treatment for Alzheimer's disease

This section discusses supplements that can be of assistance in treating AD (see Table 1).

In AD, supplementation with sodium molybdate will be of assistance. SUOX, which detoxifies sulfites, is a molybdenum-containing protein (Kappler and Enemark, 2015). Sulfites adversely affect glutaminergic neurotransmission (Zhang et al., 2004; Oztürk et al., 2006; Parmeggiani et al., 2015). Sodium molybdate by decreasing sulfite levels in AD will improve glutaminergic neurotransmission in AD and thereby improve learning and memory in AD. Activities of xanthine dehydrogenase/oxidase and SUOX in the liver of female rats and xanthine dehydrogenase/oxidase in small intestinal mucosa of female rats were significantly increased by supplementation with sodium molybdate (Wang et al., 1992). No research to our knowledge shows that molybdenum glycinate is effective in increasing levels of molybdenum-containing proteins so molybdenum glycinate is not supplemented. The tolerable upper intake level (UL) for molybdenum set by the Institute of Medicine (US) was set at 2000 μg/day (Institute of Medicine (US) Panel on Micronutrients, 2001). Given the limited clinical experience with sodium molybdate dosages of molybdenum from sodium molybdate should be limited to not more than 1000 μg/day.

Supplementation with Se-methylselenocysteine will be useful in the treatment of AD. Supplemental

Se-methylselenocysteine will increase levels of selenoproteins. Apathy, wandering, and aberrant motor behavior in AD could arise due to diffuse oxidant attacks on brains of individuals with AD, arising from deficits in selenoproteins, whereby purposeless behaviors result. Research indicates that apathy is present in 41% of patients with AD and wandering is present in 19% of individuals with AD (Lyketsos et al., 2000). Another study on AD indicates that apathy is present in 72% of patients with AD and aberrant motor behavior is present in 38% of patients where apathy and aberrant motor behavior are positively correlated with declines in cognition (Mega et al., 1996). A metanalysis indicates that apathy is present in 42% of patients with AD while aberrant motor behaviors were present in 32% of patients with AD (Zhao et al., 2016). Se-methylselenocysteine is a form of selenium whose metabolism does not depend on enzymes in the trans-sulfuration pathway. L-selenomethionine is metabolized by enzymes in the trans-sulfuration pathway (Burk and Hill, 2015). In AD supplementation with selenomethionine is avoided as selenium from L-selenomethionine can be not used to synthesize selenoproteins effectively as the trans-sulfuration pathway is dysregulated in AD. Enzymes not in the trans-sulfuration pathway can metabolize Se-methylselenocysteine so selenium in Se-methylselenocysteine can be used in AD to synthesize selenoproteins. Se-methylselenocysteine can be metabolized by kynureninase which catalyzes beta-eliminations (Rooseboom et al., 2002). No toxicity was seen in a trial of Se-methylselenocysteine that lasted 84 days at dosages of Se-methylselenocysteine of up to 800 μg a day (Marshall et al., 2017). Inorganic forms of selenium are more toxic than organic forms of selenium so sodium selenite and sodium selenate are not supplemented. Research suggests that Se-methylselenocysteine has anticancer properties that are superior to other forms of selenium (Medina et al., 2001). The UL for selenium was set at 400 μg/day by the Institute of Medicine (US) (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000).

Taurine will be a useful supplement in the treatment of AD. Activities of CBS and CTH are increased and H_2S levels are increased by supplemental taurine (Sun et al., 2016). Supplemental taurine decreases plasma homocysteine levels (Ahn, 2009). Cardiovascular risks are inversely associated with taurine (Yamori et al., 2010). The longevity of the Japanese could be due to high levels of taurine in the Japanese diet (Yamori et al., 2009). Toxicity of L-cysteine containing supplements is high (Baker, 2006). L-cysteine containing supplements are not supplemented. The cystine/glutamate antiporter transports cystine into cells while at the same time transporting glutamate out of cells (Bridges et al., 2012). L-cysteine could have to enter cells as cystine via the cystine/glutamate antiporter so glutamate is transported out of cells. Supplements that increase activity of trans-sulfuration pathway could also improve memory by increasing cystine levels as the cystine/glutamate antiporter when transporting cystine into cells also transports glutamate out of cells whereby glutamate can be used extracellularly by glutamate receptors. Supplementation with either N-acetylcysteine or lipoic acid is avoided. Increases in L-cysteine levels due to supplementation with N-acetyl-l-cysteine (Whillier et al., 2009) or alpha lipoic acid (Han et al., 1997) result from decreases in cystine levels. Pantothenic acid is not supplemented. Pantethine, a precursor of CoA synthesized from pantothenic acid, decreases cystine levels by increasing levels of cysteamine (Butler and Zatz, 1984). The observed safe level for taurine is 3 g a day (Shao and Hathcock, 2008).

Supplementation with a 1:1 L/arginine/ L-citrulline combination will be of assistance. L-citrulline is a precursor of L-arginine. Supplementation with L-arginine increases the activity of CTH (Shi et al., 2006; Yanfei et al., 2006). L-citrulline bypasses the livers, is converted into L-arginine in kidneys, and does not give spikes in nitric oxide as supplemental L-arginine does (Papadia et al., 2018). A 1:1 combination of L-arginine and L-citrulline will supply L-arginine both hepatically and extrahepatically. The observed safe level for L-arginine is 20 g a day (Shao and Hathcock, 2008).

Supplementation with heme iron polypeptide is important for the treatment of AD. With increased levels of iron ACO1 acts as an aconitase due to gaining a 4Fe-4S iron-sulfur cluster (Haile et al., 1992). Fe^{+3} is reduced to Fe^{+2} by duodenal cytochrome b (DCYTB) whereby the divalent metal transporter 1 (DMT1) can transport reduced nonheme iron (Wang and Pantopoulos, 2011). HIF2α induces transcription of DCYTB and DMT1 (Shah et al., 2009), however, mRNA transcripts of HIF2α are destabilized when bound with IRP1 (Anderson et al., 2013). With IRP1 levels high mRNA transcripts of HIF2α will be degraded which will decrease transcription of DCYTB and DMT1 induced by HIF2α by which nonheme iron absorption will be reduced. With IRP1 dysregulated a form of iron that bypasses DCYTB and DMT1 must be supplemented. Absorption of heme iron does not depend on DCYTB and DMT1. Supplemental heme iron polypeptide will support formation of iron-sulfur clusters, the activity of ACO1 as an aconitase and OXPHOS which is highly dependent on iron-sulfur proteins. OXPHOS generates ATP. Extracellular ATP is required for long-term potentiation which is required for memory formation (Fujii, 2004) so enhancing

OXPHOS, which generates ATP, could improve memory in AD. Heme iron polypeptide is a safe and effective treatment for anemia (Abdelazim et al., 2018).

Copper from copper gluconate will be helpful in AD. Copper ferroxidases are required for iron transport (Frazer and Anderson, 2014; Jiang et al., 2015). In AD, due to high levels of IRP1 copper transport could be dysregulated. Copper is also required for cytochrome c oxidase (Horn and Barrientos, 2008) which is decreased in AD (Cardoso et al., 2004). Copper glycinate is avoided as almost no research has been done on how supplementation with copper glycinate affects humans. The Institute of Medicine (US) has set the UL level for copper at 10 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001).

Coenzyme Q10 will be a useful supplement. Coenzyme Q10 is a cofactor for NADH dehydrogenase (Sharma et al., 2009), which has iron-sulfur clusters, and is dysregulated in AD. Ubiquinol is synthesized from coenzyme Q10. Ubiquinol is not supplemented. Supplementation with coenzyme Q10 will support oxidative phosphorylation. Research indicates that in dosages as high as 2400 mg a day, coenzyme Q10 is safe and well tolerated (Huntington Study Group Pre2CARE Investigators, 2010).

Supplementation with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oils where EPA levels are >60% of total EPA and DHA and which will be of assistance. Beta-oxidation of fatty acids supports OXPHOS (Wang et al., 2010; Lim et al., 2018). Eicosapentaenoic acid, but not DHA increases mitochondrial beta-oxidation (Willumsen et al., 1999). A meta-analysis indicates that EPA and DHA are effective in depression given EPA levels are >60% of total EPA and DHA (Liao et al., 2019). Some 3 g of fish oils a day is generally recognized as safe (Drugs and Lactation Database, 2006). Eicosapentaenoic acid and DHA will synergize with other supplements in the proposed treatment.

Supplementation with whey protein will be helpful. The whey protein contains high levels of glutamic acid. 2-oxoglutarate is synthesized from glutamic acid by glutamate dehydrogenase (Mkrtchyan et al., 2018). Supplementation with whey protein will increase 2-oxoglutarate levels. It also contains cystine. Supplementation with whey protein increases glutathione levels (Grey et al., 2003). Supplemental whey protein will also support increased protein synthesis.Whey protein is frequently supplemented (Pasiakos et al., 2015). Excessively high protein intake should be avoided.

In the treatment of AD vitamin B6 will be of assistance. Enzymes involved in L-cysteine metabolism, for example, CBS, CTH, and cysteine desulfurase, are frequently vitamin B6 dependent enzymes. Many enzymes involved in selenium metabolism are also vitamin B6 dependent enzymes (Soda et al., 1999). The Institute of Medicine (US) set the UL level for adults for vitamin B6 at 100 mg/day (Institute of Medicine, 1998).

Supplementation with vitamin E, beta-carotene, flavonoids, vitamin C, L-carnitine, or acetyl-l-carnitine is avoided as molybdenum-containing enzymes are oxidases. Activity of molybdenum-containing proteins such as SUOX and XO could be decreased by antioxidants. Levels of XO are decreased by vitamin E (Raghuvanshi et al., 2005). Xanthine oxidase is inhibited by quercetin which is a flavonoid (Zhang et al., 2016). Acetyl-l-carnitine decreases levels of XO (Di Giacomo et al., 1993). Vitamin C can inhibit absorption of copper (Finley and Cerklewski, 1983). Riboflavin is not supplemented. Flavin reductase, which reduces riboflavin is biliverdin reductase B (Cunningham et al., 2000). Biliverdin reductase B is part of the heme degradation pathway (Whitby et al., 2002). Riboflavin supplementation could competitively inhibit biliverdin reductase B, dysregulating heme degradation, which could dysregulate iron metabolism. Zinc is not supplemented. Metallothionein levels are increased by zinc (Cousins, 1983). Metallothionein is an L-cysteine rich protein. Supplementation with zinc could shift L-cysteine to metallothionein and away from other uses. N-acetyl-L-cysteine, lipoic acid, and pantothenic acid are not supplemented as N-acetyl-L-cysteine, lipoic acid, and/or pantothenic acid could decrease cystine levels. Manganese levels should be monitored. The DMT1 transports both iron and manganese (Wolff et al., 2018). Manganese would be supplemented if manganese levels are low. The UL limit for manganese set by the Institute of Medicine is 11 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001). Manganese glycinate would not be supplemented as to our knowledge no clinical trials of manganese glycinate were undertaken on humans.

Once AD has developed, all the supplements in the proposed treatment may be required. Before any cognitive impairment has occurred supplementing with only sodium molybdate and Se-methylselenocysteine could significantly decrease risks of developing AD. Once the treatment is shown to be effective appropriate supplement formulations could reduce the number of pills that have to be taken. The research presented clarifies safety profiles of suggested supplements (Table 2).

Conclusion

In AD there are high homocysteine levels where severity of AD is positively correlated with homocysteine levels.

Table 2: Research presented to clarify safety profiles of suggested supplements.

Supplement	Research that addresses safety of recommended supplements
Sodium molybdate	The Institute of Medicine set the tolerable upper intake level (UL) limit for adult humans at 2000 μg/day (Institute of Medicine (US) Panel on Micronutrients, 2001)
Se-methylselenocysteine	The Institute of Medicine set the UL limit for adult humans at 400 μg day (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000)
Taurine	Observed safe level is 3 g/day (Shao and Hathcock, 2008)
L-arginine	Observed safe level is 20 g/day (Shao and Hathcock, 2008)
Iron from heme iron polypeptide	Effective and safe treatment for anemia (Abdelazim et al., 2018)
Copper from copper gluconate	The Institute of Medicine has set the tolerable UL for adult humans at 10 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001)
Coenzyme Q10	Well tolerated at dosages as high as 2400 mg/day (Huntington, 2010)
Eicosapentaenoic acid (EPA)	3 g of fish oils a day is generally recognized as safe (Drugs and Lactation Database, 2006)
Whey protein	Is frequently supplemented (Pasiakos et al., 2015). Proteins intakes that are excessive should be avoided
Vitamin B6	The Institute of Medicine has set the tolerable UL limit for adults at 100 mg/day (Institute of Medicine, 1998)

We have cited some references of clinical trials undertaken on humans. One exception is molybdenum where most studies done on animals with findings then extrapolated to humans. The Institute of Medicine (US) is associated with the National Academy of Sciences (US). The Institute of Medicine is now termed the National Academy of Medicine (US).

High homocysteine levels in AD indicate that activity of the trans-sulfuration pathway, which metabolizes homocysteine, is low in AD. L-cysteine is synthesized by the trans-sulfuration pathway. With low levels of L-cysteine due to low activity of the trans-sulfuration pathway, pathways downstream from L-cysteine synthesis will be dysregulated. SUOX levels will be decreased, synthesis of glutathione will be decreased, synthesis of CoA will be decreased which will decrease synthesis of acetylcholine and iron-sulfur cluster formation will be decreased which will dysregulate OXPHOS and iron metabolism. Low activity of the trans-sulfuration pathway also dysregulates selenoproteins which leads to oxidant stress in AD. There are epigenetic dysregulations in AD due to a lack of 2-oxoglutarate, which is required both for TET enzymes which demethylate DNA and JumonjiC-domain containing proteins which demethylate histones, and due to oxidant stress resulting from dysregulations of selenoproteins. An initial perturbation if prevented from occurring could stop AD from developing but once there has been cognitive decline there already could be epigenetic changes whereby correcting the initial perturbation would not be enough to stop the cognitive decline.

Treatments now available for AD only modestly affect symptoms and do not slow or fundamentally alter the course of the illness. The treatment proposed could be a disease-modifying treatment in AD as biological pathways at the headwaters of the biological dysregulations in AD are being addressed. The etiology proposed for AD by this paper could open up lines of research that could lead to a better understanding of AD and better treatment of AD.

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