

THEORETICAL ARTICLE

Does thiamine protect the brain from iron overload and alcohol-related dementia?

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Abstract

Alcohol-related dementia (ARD) is a common and severe co-morbidity in alcohol use disorder (AUD). We propose brain iron overload (BIO) to be an important and previously neglected pathogenic process, accelerating cognitive decline in AUD. Furthermore, we suggest thiamine, which is frequently depleted in AUD, to be a key modulator in this process: Thiamine deficiency impairs the integrity of the blood-brain barrier, thereby enabling iron to pass through and accumulate in the brain. This hypothesis is based on findings from animal, translational, and neuroimaging studies, discussed in this article. To validate this hypothesis, translational studies focusing on brain iron homeostasis in AUD, as well as prospective clinical studies investigating prevalence and clinical impact of BIO in AUD, should be conducted. If proven right, this would change the understanding of ARD and may lead to novel therapeutic interventions in prevention and treatment of ARD.

KEYWORDS

alcohol use disorder, blood-brain barrier, brain iron accumulation, cognitive decline, dementia, neurodegeneration, neurotoxicity, thiamine

1 | INTRODUCTION

Presenile cognitive decline is frequently seen in patients with alcohol use disorder (AUD) and has been referred to as a “21st-century silent epidemic” due to increasing rates of alcohol consumption in recent years. Furthermore, AUD is accountable for a considerable amount of disease burden^{1,2}; AUD is postulated to be responsible for \approx 6.8% of global disability-adjusted life-years (DALYs) for males and 1.6% of global DALYs for females. In addition, there is strong evidence that the burden of disease increases with increasing alcohol consumption.³ However, large cohort studies examining the association between alcohol consumption and dementia risk revealed a U-shaped association, with moderate drinking patterns being associated with a decreased risk for dementia when compared with total abstinence, whereas heavy alcohol consumption inferred a markedly increased risk

for dementia.^{4,5} Although the underlying pathophysiologic pathways, potentially leading to neurodegeneration in AUD, are not fully understood, thiamine deficiency and other dietary deficits as well as ethanol itself and its metabolites, particularly acetaldehyde, are known to exert neurotoxic effects.⁶ Pathomorphological correlates of neurodegeneration associated with chronic alcohol abuse consist of atrophy of specific regions of the brain, for example, hippocampus and cerebellar vermis, and general brain atrophy, accompanied by an increase of cerebrospinal fluid.⁷⁻⁹ These neurodegenerative processes are primarily hypothesized to be caused by direct neurotoxic effects of alcohol; however, additional indirect pathways promoting white matter degeneration exist: Among others, ethanol-induced neuroinflammation is associated with deterioration of myelin sheaths and impairment of myelin synthesis.¹⁰ Furthermore, alcohol-induced liver damage imposes, via the liver-brain-axis, additional oxidative stress onto the brain.¹¹

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2 | BRAIN IRON OVERLOAD AND THIAMINE HYPOTHESIS

We hypothesize that excess iron, that is, brain iron overload (BIO), is a highly relevant pathway leading to cognitive deterioration in individuals with AUD. We further hypothesize thiamine depletion, a common concomitant feature in AUD patients, to be a key stimulus for BIO, as thiamine deficiency disrupts the integrity of the blood-brain barrier (BBB), enabling iron from the circulation to enter the brain in an uncontrolled manner.

3 | SUPPORTING THE HYPOTHESIS

On a cellular and biochemical level, iron overload and subsequent lipid peroxidation may lead to ferroptosis as an iron-dependent form of necrosis.¹² Furthermore, increased iron levels can lead to oxidative stress and activation of macrophages, culminating in fibrosis as well as necrosis.¹³

These phenomena can be observed in different tissues resulting in considerable damage to a multitude of organs. Research has mainly been focusing on iron-related damage to the liver.¹⁴⁻¹⁸ However, the brain is highly susceptible to damage due to iron overload as well. Iron accumulation in the brain has been found to impair cognitive function in various neurodegenerative diseases and is specifically implicated in the pathogenesis of Alzheimer's disease (AD): increased levels of iron and other metal ions have been shown to be involved in the development of AD and are reported to be elevated in brain tissue of individuals with AD.^{19,20} This iron dyshomeostasis results in altered neuronal metabolism and oxidative stress and affects plaque deposition of amyloid beta (A β) protein.²¹⁻²⁵ Furthermore, pharmaceutical reduction of brain iron level has proven to be successful in animal models²⁶⁻²⁸ and has recently been discussed as a promising therapeutic target in humans.²⁹ A direct neurodegenerative effect of BIO has also been proven for another group of diseases named neurodegeneration with brain iron accumulation (NBIA).³⁰ However, even in healthy individuals, high striatal iron was found to be a predictive biomarker for cognitive decline in normal aging.³¹

Patients with AUD commonly present with an altered iron homeostasis caused by several mechanisms including a lower expression of hepcidin, which is a key molecule in iron homeostasis. Increased intestinal iron absorption in individuals with AUD results from a higher intestinal permeability induced by alcohol.³²⁻³⁴ These processes are substantial contributing factors in the emergence of liver damage in AUD patients, eventually leading to liver fibrosis and cirrhosis in the most severe cases.^{13,35} In contrast to these heavily addressed devastating effects of excess liver iron, the sequelae of BIO in this particular group of patients has hardly been subject of research so far. To the best of our knowledge, only one study addressed the presence and degree of BIO in AUD patients in vivo: Juhás et al. analyzed iron-sensitive quantitative susceptibility maps, reconstructed from standard brain functional MRI (fMRI) data. When comparing 20 patients

Highlights

- Presenile cognitive decline is a very common consequence of alcohol use disorder.
- The underlying pathophysiologic pathways are not yet fully understood.
- Brain iron accumulation may contribute to the emergence of alcohol-related dementia (ARD).
- Thiamine could play a crucial role in protecting the brain from excess iron.
- Further research is needed to better understand ARD.

Research in Context

1. Systematic review: The authors conducted a literature review using traditional (eg, MEDLINE/PubMed) sources. The significance of brain iron overload (BIO) in alcohol-related dementia (ARD) has not been researched thoroughly. However, research exists that examines BIO in other neurodegenerative diseases as well as studies showing the consequences of thiamine deficiency. These relevant citations are summarized and discussed.
2. Interpretation: Based on previous studies, an integrated hypothesis is proposed, explaining the role of BIO in ARD. This hypothesis provides an explanation for frequent clinical observations and suggests novel approaches for prevention and treatment of ARD.
3. Future directions: This article provides a foundation for future research and points out major remaining questions. For example (a) quantitative assessment of BIO in ARD (b) exact mechanisms leading to disruption of the blood-brain barrier in the circumstance of thiamine deficiency, and (c) the reversibility of cognitive dysfunction through administration of thiamine.

with AUD with a mean alcohol dependence duration of 16 years to 15 age- and sex-matched healthy controls, they found significant brain iron accumulation in AUD patients.³⁶ Consistent increases of iron were found in all studied deep gray matter regions in individuals with AUD. The observed increases were statistically significant in the striatum, globus pallidus, and cerebellar dentate nucleus, which are also the brain regions with the strongest age-dependent iron accumulation in the brains of healthy people without neurological disease, that is, the "hot spots" of physiological brain iron accumulation.³⁷

Considering these findings, we additionally propose that thiamine has a significant modifying role in the development of BIO in alcohol-dependent individuals. Thiamine, also known as vitamin B1, is water-soluble and plays an important role as an enzyme cofactor

in the metabolism of carbohydrates and branched amino acids. It is also elementary for neural functioning.³⁸ Thiamine deficiency has been observed in up to 80% of alcohol-dependent individuals due to inadequate dietary intake, reduced gastrointestinal absorption, and reduced activation of thiamine into the biologically active form thiamine pyrophosphate due to impaired liver function.³⁹⁻⁴¹ In addition, a diet dominated by alcohol is high in calories but consists of low nutritional value, which further increases demand for thiamine.⁴² However, we believe that due to depleted thiamine levels in patients with AUD, the brain is vulnerable to iron accumulation, as thiamine depletion was shown to induce a higher permeability of the BBB in animal models, hereby leading to unregulated iron transit across the BBB: Harata and Iwasaki⁴³ demonstrated a breakdown of the BBB in rodents treated with a BBB-permeant thiamine antagonist (eg, pyrithiamine) when compared to both a control group (placebo) and a group treated with a BBB-impermeant thiamine antagonist (eg, oxythiamine). Following 8 days of daily peritoneal administration, rodents receiving the BBB-permeant thiamine antagonist developed symptoms of neurodegeneration. After completion of 10 days, histological lesions as well as extravasation of albumin were detected in the thiamine-deficient animals in contrast to those receiving oxythiamine or placebo, indicating the crucial role of thiamine with regard to preserving the integrity of the BBB. Endothelial dysfunction seems to be essential in this process, causing vascular leakage and excess iron accumulation in perivascular microglia, eventually leading to an upregulation of pro-inflammatory microglial inducible nitric oxide synthase (iNOS) in the brain and increased levels of oxidative stress.⁴⁴ Furthermore, thiamine is a known modulator of neuroinflammation, scavenging reactive oxidative species, which are further augmented by elevated iron levels upon thiamine depletion.⁴⁵

A further common medical condition, postulated to be associated with BIO as well as thiamine deficiency, is obesity.⁴⁶ A preliminary case-control neuroimaging study provides evidence for a positive association between iron load in gray matter regions and obesity, as well as insulin resistance.⁴⁷ In addition, there are studies reporting an association between long-term glucose levels and elevated risk for dementia. Unfortunately, in these studies thiamine levels, iron status, and neuroimaging data were not analyzed.^{48,49} Conjoined, these results may indicate thiamine deficiency, as well as resulting BIO and cognitive decline to be present in absence of AUD. Furthermore, these results implicate presenile cognitive decline in AUD patients to not be exclusively caused by direct neurotoxic effects of alcohol.

Another relevant aspect, with regard to thiamine deficiency, is its pathogenetic link to Wernicke encephalopathy, a potentially life-threatening condition, which is considered to be greatly underdiagnosed.^{50,51} Typical symptoms of Wernicke encephalopathy include the triad of confusion, ophthalmoplegia, and ataxia. These symptoms are, at least partially, congruent with clinical signs of the NBIA group of diseases, where early symptoms may include neuropsychiatric symptoms, gait abnormality, and mild global developmental delay, whereas parkinsonism is dominant in the later stages of these progressing group of diseases, indicating that similar pathogenetic mechanisms might be the underlying cause in both entities.⁵²

Moreover, our hypothesis may well explain the absence of iron-induced neurological or psychiatric symptoms in medical conditions, in which systemic iron overload is not accompanied by thiamine depletion. For example, in individuals with hereditary hemochromatosis, several organs, most prominently the liver, are impaired by excess iron levels; however, symptoms of the central nervous system (CNS) are very uncommon.⁵³ In other words, in hereditary hemochromatosis alone, systemic iron overload does not lead to brain iron accumulation and subsequent neurodegeneration, as normal thiamine levels protect the brain, but not the liver, by sustaining a functional BBB.

4 | TESTING THE HYPOTHESIS

We believe that the following steps are warranted regarding the presented hypothesis. First, it is essential to collect reliable data on the real prevalence of BIO in AUD and to investigate in prospective studies to what extent the decline in cognitive function can be explained by brain iron accumulation. Second, translational studies investigating underlying pathophysiological pathways involved in brain iron accumulation should clarify the precise role of thiamine in this process and aim for answers to the following questions: What are the exact points of action causing BBB damage in the circumstance of thiamine deficiency? Which role does peripheral thiamine status play, compared to brain thiamine levels? And to what extent, if at all, is existing CNS damage reversible through the administration of thiamine?

Both clinical and translational studies will not only have the potential to deepen our understanding of brain iron acquisition in health and disease but might lead to implementation of novel therapeutic interventions for the prevention and/or treatment of dementia in AUD, like evaluating the use of chelators to reduce brain iron levels.^{23,29} In addition, there is substantial need for further studies with regard to application form, dosage, and duration of thiamine substitution in individuals with alcohol dependence, as there is lack of evidence and subsequently of recommendations regarding use of thiamine as a preventative measure before, during, and after alcohol withdrawal. A recent Cochrane Review investigating data on thiamine substitution in patients with alcohol abuse could identify only two randomized controlled trials, of which only one contained sufficient data for quantitative analysis.⁵⁴

We believe that further research in the prevention of alcohol-attributed dementia, by investigating the role of brain iron accumulation and thiamine in AUD, is of the utmost importance to better define and implement more effective treatment recommendations in the near future.

5 | CONCLUSION

In summary, previous findings lead us to the hypothesis that iron accumulation in the brain due to the breakdown of the BBB evoked by thiamine depletion may be a previously unrecognized factor in the pathogenesis of alcohol-related dementia. Because BIO in AUD was found in deep gray matter nuclei that were already showing

considerable physiological age-related iron accumulation, it seems plausible that AUD leads to an enhancement or deregulation of physiological brain iron acquisition pathways.

If our hypothesis were true, this would implicate that iron metabolism should be considered as a relevant factor in the management of AUD patients. Furthermore, this would implicate the emergence of possible new therapeutic approaches in the treatment of cognitive decline in AUD patients, raising hope for the quest of preventing, or at least limiting, the progression of alcohol-related dementia.

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CONFLICTS OF INTEREST

We have no conflicts of interest to declare.

AUTHORS CONTRIBUTION

All authors contributed equally in the writing process and to literature research.

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