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Towards the prevention of potential aluminum toxic effects and an effective treatment for Alzheimer's disease

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ABSTRACT

In 1991, treatment with low dose intramuscular desferrioxamine (DFO), a trivalent chelator that can remove excessive iron and/or aluminum from the body, was reported to slow the progression of Alzheimer's disease (AD) by a factor of two. Twenty years later this promising trial has not been followed up and why this treatment worked still is not clear. In this critical interdisciplinary review, we provide an overview of the complexities of AD and involvement of metal ions, and revisit the neglected DFO trial. We discuss research done by us and others that is helping to explain involvement of metal ion catalyzed production of reactive oxygen species in the pathogenesis of AD, and emerging strategies for inhibition of metal-ion toxicity. Highlighted are insights to be considered in the quests to prevent potentially toxic effects of aluminum toxicity and prevention and intervention in AD.

1. Evidence

1.1. The complex multifactorial nature of Alzheimer's disease

Alzheimer's disease [AD] is the most common form of dementia, accounting for 60–70% of cases of neurological impairment in the elderly [1]. After the age of 65, its prevalence approximately doubles every five years [2]. In 2001, the prevalence of dementia in persons over age 60 was estimated by a Delphi consensus method to range from 1.6 to 6.6% [3,4]. By 2040, the total number of people in the world with dementia is expected to more than triple relative to the number affected in 2001 [3,4]. AD affects the brain's ability to perform daily activities and to control thought, memory and language [5–8]. The disorder is associated with gross changes in the brain and changes at the microscopic levels [4–6,8,9]. At the macroscopic level, AD brains are smaller than normal, folding of the cortex is decreased, and ventricle size is increased. At the microscopic level, neuron count and synapse density are decreased, and the brain is riddled with amyloid plaques (diffuse and neuritic) containing amyloid-beta (Aβ) peptides, a secretase-mediated breakdown product of the amyloid precursor protein (APP), and neurofibrillary tangles containing excessive amounts of hyperphosphorylated tau protein [1,4,8,9].

The AD brain also is characterized by markers of oxidative stress, neuroinflammation and dysregulated inflammatory signaling (Section 1.3). The term *oxidative stress* refers to an imbalance between the body's production of free radicals and their neutralization by a number of different means [10,11]. It may occur as the result of excessive ROS production, reduced antioxidant defense or a combination of both. All of these processes may be relevant in AD. It has been suggested that high energy demand from dependence on oxidative metabolism plus a high concentration of polyunsaturated fatty acids, and relatively low antioxidant enzyme activity, render the brain more vulnerable to oxidative insult than most organs [12]. The term *neuroinflammation* refers to the "integrated response of all cells within the central nervous system, including the neurons, macroglia, microglia and infiltrating leukocytes" to both acute and pathological insults (pg 237) [13]. Neuroinflammation can be a cause or a consequence of excessive oxidative stress [13–18]. Different types of central nervous system or systemic infections also have been implicated in AD (Table 2) [19–27]. As well, there is increasing recognition that epigenetic processes are involved in AD and other neurodegenerative diseases [28,29]. The term *epigenetic* literally means "above" genetics, and refers to processes that affect the expression of particular genes in DNA but do not change the linear

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Table 1
Major risk factors for sporadic Alzheimer's disease.[a]
Adapted from Prasher et al. [9].

Increasing age
Predisposing genetic factors
• Gender; E4 allele of ApoE; other gene variants; Down syndrome; family history of AD
Environmental factors
• Years of education; second language (protective)
• Head injury (predisposing)
Predisposing metabolic abnormalities
• Diabetes; cardiovascular or cerebrovascular disease

[a] Factors listed here are ones that might be controlled for in epidemiological studies of Alzheimer's disease or in clinical treatment or prevention trials in the opinion of the authors. As indicated in Table 2, various infections also are implicated in AD, though this topic is controversial.

sequence of its nucleotides. Epigenetic processes include methylation of DNA, alteration of the degree of chromosome compaction as the result of modification to the tails of DNA-binding histone proteins, and regulation of gene expression by non-coding RNAs such as micro RNAs (miRNAs) [28]. Certain brain-abundant miRNAs, such as miRNA-125b and miRNA-146a, found to be specifically elevated in AD brain, are also up-regulated in aluminum-stressed human brain cells in primary culture [30, JIB, in press (this current journal)].

There is evidence for involvement of metal ions in AD pathogenesis, though this is complex [31,32]. AD brain is characterized by unusual distribution of metal ions, including iron, copper, zinc [31–33], and aluminum [34–36] in regions that are degenerating. However, there is controversy as to whether average concentrations of these metals are significantly altered in particular brain regions [37–39]. Furthermore, although complexes of Aβ and redox metals, especially iron, can be sources of reactive oxygen species (ROS) production in vitro [40], it has been argued that metal iron binding by Aβ may play a protective role in vivo [41]. Brain changes characteristic of advanced AD are likely not reversible [42].

Risk factors for the sporadic form of AD, which accounts for approximately 95% of cases [4,9], include the aging process in combination with interaction between various genetic, metabolic and environmental factors [4,9] (Table 1). The E4 allele of apolipoprotein E, the major lipid carrier in the central nervous system, has been consistently identified as the major genetic risk factor for AD, although it is not specific for this disorder [43–45]. Other genetic factors also are involved in AD [4,9]. The impact of E4 on disease risk may, in part, be due to its influence on oxidative and/or immuno-inflammatory status [46]. Interest in iron, copper and zinc in AD is topical [31–33,40]. Although aluminum involvement in AD is still considered controversial, studies in various model systems continue to reveal toxic effects from aluminum exposures equivalent to those experienced by humans in daily living [39,47–50]. See also various publications in this issue.

Efforts to develop an effective treatment for AD have remained elusive. Drugs currently licensed for use temporarily slow disease progression in some affected individuals but there is no evidence that they delay or prevent onset of AD [4,42,51]. The reduction of oxidative stress has been a therapy target in clinical trials, but results have largely been negative, or mild at best [9,52,53] (See other sources for approaches currently being considered in AD [4,9,54–60].). While it is clear that oxidative stress is playing some contributory role to the AD process [40], oxidative stress alone is likely not the only pathological insult that needs to be targetted. We have shown that chelator/antioxidant combinations are synergistically more effective than single chelators or antioxidants in antioxidant therapy approaches in metallo-based in vitro models of AD [61,62] (see Section 1.4). The rationale for this combined approach was based, in part, on results from a promising but neglected clinical trial of a trivalent metal ion chelator called desferrioxamine in AD [63,64] (Fig. 1), and on known properties of this chelator, which include not only metal sequestering but also generation of radicals [65–71] (Table 3). The clinical trial of DFO is discussed next.

Table 2
Different infections implicated in Alzheimer's disease.*

Agent	Reference
Herpes simplex virus 1	[19–21]
Chlamydia pneumoniae	[22,23]
Toxoplasma gondii	[24]
Spirochetes	[25]
*Helicobacter pylori***	[26]
Other agents	[27]

* Involvement of these infections is considered controversial as of 2011.
** Treating helicobacter for 5 years significantly deterred development of dementia in a population with a relatively low infection prevalence.

1.2. The successful but neglected 1991 trial of desferrioxamine in Alzheimer's disease revisited

In 1991, the intramuscular injection of low dose desferrioxamine mesylate (DFO; desferoxamine; deferoxamine; Desferal) was found to reduce the rate of progression of AD by a factor of two within a two-year period [63]. Furthermore, among 48 patients in the study,

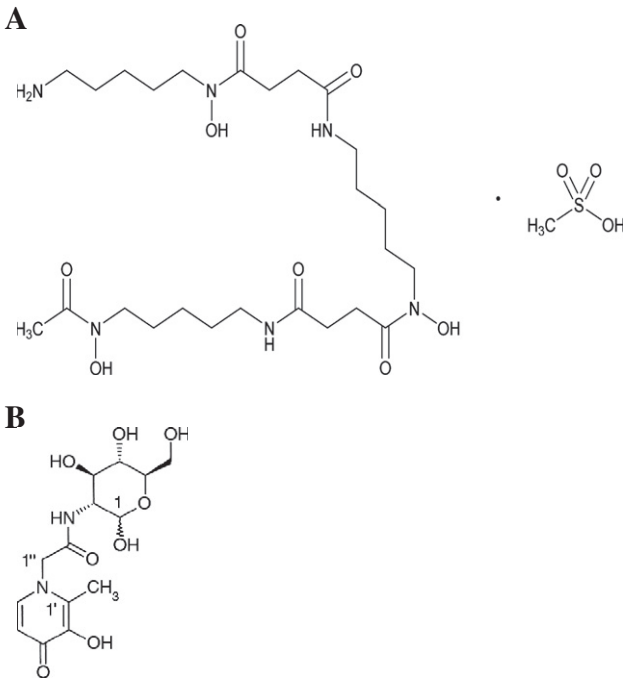

Fig. 1. Structures of desferrioxamine and Feralex-G. (A): DFO: deferrioxamine mesylate (USAN); alternatively desferrioxamine mesilate (BAN). DFO is a commercially available siderophore (molecule that sequesters iron from the environment) produced by *Streptomyces pilosus*. It is a hexadentate chelator, and binds trivalent iron or aluminum in a 1:1 ratio. It is used in many countries in the mesylate form to treat various forms of iron overload, and also aluminum overload. A major drawback to its use is that it is effective only when administered parenterally [65]. Image kindly provided by Andrzej Wilk, PhD, Senior Scientific Liaison, US Pharmacopeia; CAS Number 138-14-7; DFO has a molecular formula of $C_{25}H_{48}N_6O_8 \cdot CH_4O_3S$; MW 657. (B): Feralex-G. Feralex-G is an experimental oral chelator made from three natural substances—glucosamine (1), an amino acid, glycine (1″) and maltol (1′) [76]. It was designed to enter cells via complexing of the glucosamine "tail" with glucose transporters, and to be a safe replacement for DFO which is effective only parenterally (i.e., by intramuscular, subcutaneous, or intravenous routes). Feralex-G is bidentate and complexes with trivalent metal ions in the ratio of 3:1. Hydrophilicity of Feralex can be altered by substitution of the amino acid linker. Image reproduced from Kruck et al. [61] with permission. Feralex-G has a molecular formula of $C_{13}H_{13}N_2O_7$; MW 344 [61,62,76].