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Lithium may be useful in the prevention of Alzheimer's disease in individuals at risk of presenile familial Alzheimer's disease

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Summary Alzheimer's disease (AD) is the most common form of dementia among older people. Presenile familial AD (FAD) and sporadic Alzheimer's disease (SAD) have identical brain lesions, containing senile plaques with beta-amyloid (Abeta) peptide and neurofibrillary tangles formed by hyperphosphorylation of a microtubule-associated protein known as tau. However, FAD and SAD differ in onset and genetic transmission. Unlike SAD, presenile FAD is transmitted as a pure autosomal dominant trait. The authors suggest that lithium could be used for AD prevention, particularly in individuals at risk of presenile FAD, which has early onset. Evidence supporting this hypothesis suggests that lithium decreases Abeta peptide production and inhibits the activity of glycogen synthase kinase-3 which induces aggregation of tau protein into tangles, and tau hyperphosphorylation. Prevalence of AD is lower in patients with chronic lithium treatment, which also increases brain-derived neurotrophic factor activity, so might prevent onset in patients at risk for AD. Several considerations are suggested for prevention trials: the effect of lithium could be evaluated in young animal models that express presenile FAD mutant genes; the time, dose, duration and monitoring of lithium therapy are considered; early phenotypes could be monitored for treatment effect; and some other agents, like valproic acid, could also be candidates for prevention.
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Introduction

Alzheimer's disease (AD), a complex disease with neurodegenerative changes, is the most common form of dementia among older people. Most cases (90–95%) are sporadic AD (SAD), and a portion is presenile familial AD (FAD). AD has very clear neuropathological features, which include the presence of senile plaques and neurofibrillary tangles together with neuronal loss and cortical atrophy [1]. The brain lesions are identical in SAD and presenile FAD. The symptoms of AD appear years after the pathological changes commence, which

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has led neuroscientists to believe that AD is irreversible, and that the onset of dementia, around 40—60 years of age for presenile FAD and approximately over 65 years of age for SAD, is due to the accumulation of lesions [2,3].

Studies have demonstrated that the senile plaques contain beta-amyloid peptide (Abeta), which is produced by cleavage of the amyloid precursor protein (APP) by beta- and gamma-secretases. Neurofibrillary tangles are formed by hyperphosphorylation of a microtubule-associated protein known as tau, causing it to aggregate in an insoluble form. The formation of tangles and plaques is influenced by various factors including age, genetic factors, oxidative stress and inflammation [3,4]. As Abeta peptide plays a pivotal role in AD, therapeutic strategies that inhibit Abeta aggregation and promote extracellular Abeta removal are currently the focus of drug developments for managing AD [5].

While there has been great promise in the scientific understanding and early detection of AD, treatments for AD are mainly supportive, symptomatic or disease-slowing. Thus, there remains an urgent need to identify effective prevention strategies or therapies to avert this overwhelming public health problem. Although preventive treatments for AD are being actively searched for, there have been numerous difficulties in implementing prevention trials in AD, including the need for long duration and difficult follow-up because the onset of AD is late, the age onset range is large and the risk of AD for each individual is unknown. Furthermore, the long-term adverse event profile or toxicity of the agents being studied is another concern. Thus, although many prevention trials are ongoing, to date no prevention trial has successfully delayed or prevented the development of AD [6]. In this report, we suggest that lithium may be useful in the prevention of AD in individuals at risk of presenile FAD.

Presenile familial Alzheimer's disease

Epidemiological and individual case studies indicate that genetic factors play a significant role in the genesis of AD, but most researchers believe that genetic transmission of SAD is more complicated than a simple autosomal dominant trait. Nevertheless, a small proportion (around 10%) of AD cases associated with early onset is transmitted as a pure autosomal dominant trait. Studies in families multiply affected with presenile FAD have identified three genes (presenilin 1 (PS1), presenilin 2 (PS2) and beta-amyloid precursor protein (betaAPP)) associated with high-penetrance early onset FAD [7,8]. There are some advantages to studying AD prevention in individuals at risk of presenile FAD (subjects carrying pathogenic mutations in these genes) rather than in the general population. First, presenile FADs are all associated with early onset, usually between 40 and 60 years, so there would be a shorter follow-up period than such studies performed in the general population (for SAD, onset over the age of about 65 years). Second, study of AD prevention in the general population needs a large sample size and a control group is needed for comparison because we cannot know the risk of developing AD in each studied subject. In contrast, in presenile FAD, the disease is transmitted as a pure autosomal dominant Mendelian trait with almost full penetrance. Third, individuals at risk of presenile FAD could be identified by family history and genetic testing at an early age, which makes early prevention feasible. Fourth, currently there is no optimal treatment for this disease once AD symptoms develop. Once AD develops, the neurodegenerative process is probably irreversible, so early prevention of AD neuropathology (senile plaques and neurofibrillary tangles) could be a good strategy for intervention in these subjects at high risk for AD. Finally, genetically engineered animal models that express these presenile FAD mutant genes have been developed, so prevention could also be tested preclinically [9].

The hypothesis

Lithium is an effective and well-tolerated mood stabilizer used in the prevention and acute treatment of bipolar disorders. Lithium has previously been used to treat AD patients with mixed results [10—12]. As AD is an irreversible, progressive neurodegenerative disorder, once it has developed, it is difficult to recover. Here, we propose that lithium could be used for AD prevention, particularly in individuals at risk of presenile FAD. The reasons are as follows:

1. Mutations in the genes encoding PS1, PS2 and betaAPP either result in increased production of Abeta or increased production of the more fibrillogenic Abeta 1—42 peptide [13]. The aggregation and deposition of Abeta peptides are considered by many to be the crucial pathological insult that ultimately leads to the development of AD. Regulating the production and/or aggregation of Abeta peptides could therefore be of considerable benefit to patients afflicted with AD [14]. An in vitro study has found that

lithium, in a dose-dependent manner, inhibits Abeta peptide secretion in COS7 cells transfected with amyloid precursor protein C100 [15].

2. Animal studies have found that overexpression of glycogen synthase kinase-3 (GSK-3), the predominant tau-kinase in brain, induces aggregation of tau protein into tangles similar to those of AD [16]. In addition, deletion studies show that both tau and GSK-3beta, one isoform of the GSK-3 protein, bind to the same region of PS1, and mutations in PS1 that cause presenile FAD increase the ability of PS1 to bind GSK-3beta and increase its tau-directed kinase activity [17]. Lithium is a GSK-3 inhibitor and partial GSK-3 inhibition is likely to be achieved within the clinical therapeutic range [18].
3. Evidence suggests that in AD, tau proteins become hyperphosphorylated, which can contribute to neuronal degeneration. In vitro study found that lithium inhibited tau hyperphosphorylation in living neurons, suggesting that lithium treatment might slow tau phosphorylation in the brains of patients with AD [19].
4. Case-control data in elderly euthymic patients with bipolar disorder on chronic lithium therapy and similar patients without recent lithium therapy found that the prevalence of AD was lower in patients on chronic lithium treatment than patients without recent lithium treatment, suggesting a protective effect of lithium against AD in patients with bipolar disorder [20].
5. Stress and depression are known risk factors for AD. There is ample evidence suggesting that stress or depression may act by decreasing central brain-derived neurotrophic factor (BDNF) activity to increase AD risk, and agents that increase central BDNF activity could reduced the risk of AD in depressed patients [21]. Chronic lithium treatment has been shown to increase brain BDNF activity in animals [22].

The above outlines the potential use of lithium in the prevention of AD in individuals at risk of presenile FAD. Several points are suggested for the design of prevention trials.

First, the potential prevention effect of lithium in individuals at risk of presenile FAD could initially be evaluated in young animals that express presenile FAD mutant genes. A recent study reported that lithium reduces tau phosphorylation but not Abeta or working memory deficits in transgenic 3×Tg-AD mice (with three mutations in APP, tau and PS1) [23]. In the study, lithium was administered in old rather than young mice (where irreversible neurodegenerative changes have not formed). Second, we need to consider the time between beginning treatment, dose of lithium, duration and monitoring of treatment to appropriately test the present hypothesis. Third, to evaluate the lithium preventive effect, some phenotypes that develop before clinical AD symptoms in presenile FAD could be monitored. For example, regional brain hypometabolism can be identified with PET in presymptomatic presenile FAD subjects [24]. Studies of biochemical markers suggest that elevations of plasma $Abeta_{1-42}$ peptide occur early in presenile FAD subjects [25]. Finally, while this report focuses on lithium, other agents that may prevent AD could also be evaluated for potential use in individuals at risk of presenile FAD. For example, valproic acid, similar to lithium as a mood stabilizer and GSK-3 inhibitor but with milder adverse effects, was found to inhibit Abeta peptide production in HEK293 cells stably transfected with Swedish amyloid precursor protein (APP) (751) in the brains of an AD transgenic mouse model [26]. Furthermore, several agents suggested for AD prevention, including hyperforin [27], phenytoin [28] and oltipraz [29], could also be candidate agents for AD prevention in individuals at risk of presenile FAD.

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