

Invited commentary

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Lithium treatment and risk for dementia
in adults with bipolar disorder†

Calum Sutherland and Ashleigh C. Duthie

Summary

Alzheimer's disease clinical trials are failing at an alarming rate, highlighting the desperate need for novel thinking to combat this escalating health crisis. A recent large-scale population study indicates that lithium treatment reduces dementia development, supporting preclinical mechanistic evidence that this commonly used agent might be clinically valuable in dementia.

Declaration of interest

None.

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Almost 2% of the UK population has a diagnosis of dementia, and this is expected to rise to more than 2 million by 2051 (150% increase in 40 years). Alzheimer's disease is the major form of dementia (50–70%) presenting with the unique neuropathological diagnostic characteristics of amyloid plaques coupled to neurofibrillary tangles. Around 20 years ago the amyloid cascade hypothesis proposed that the generation of amyloid beta protein was the initial and central lesion leading to neuropathology, neuronal cell loss, vascular damage and ultimately the symptoms of Alzheimer's disease. There was real hope that agents targeting this cascade would provide the first therapeutics for Alzheimer's disease based on disease mechanism. Unfortunately, after many years of research and great expense, this hope has been replaced by real concern that such interventions are not leading to clinical benefit.¹ More than half of all trials of agents designed to interfere with the amyloid cascade have either failed or been halted, with very minor clinical benefit reported in studies completed to date,^{2,3} thus the amyloid cascade hypothesis is under intense scrutiny.

Alternative approaches to prevent Alzheimer's disease have not been pursued with as much vigour. However, therapeutics to prevent tangle formation have recently entered phase three clinical trials,³ and an acceptance of the importance of neuroinflammation and risk factors in dementia development have led to an interest in repurposing currently available drugs for fast tracking into dementia care. Again, the initial results of antioxidant, anti-inflammatory and anti-diabetes therapies have not been encouraging.

**Glycogen synthase kinase-3
(GSK3) as a therapeutic target**

Glycogen synthase kinase-3 (GSK3) has been proposed as a molecular link between diabetes and dementia.⁴ Although initially found as part of insulin regulation of glycogen metabolism GSK3 actually contributes to multiple biological processes in the brain.⁴ The pharmaceutical industry developed highly selective inhibitors of GSK3 to reverse the hyperglycaemia that defines diabetes. However, preclinical studies in rodents indicated that chronic GSK3 depletion is associated with hepatic toxicity, and this has greatly hindered progression to clinical trials. In more recent years attention has turned to the role of GSK3 in Alzheimer's disease.

†See pp. 46–51, this issue.

GSK3 inhibition reduces tau hyperphosphorylation, tangle formation and cognitive decline in animal models of Alzheimer's disease. GSK3 is also a regulator of amyloid precursor protein processing (Fig. 1) and thus may have an impact on both tangle and plaque generation; its other functions include regulation of brain glucose metabolism, synaptic function, neuronal development, neuroinflammation and neuronal polarity.⁴ The therapeutic potential of the GSK3 inhibitor tideglusib has recently been investigated in a small number of patients with Alzheimer's disease.⁵ There were no significant benefits on the cognitive measures in this study, however, the authors primarily focused on safety and tolerability, which were deemed acceptable at the doses used, and proposed a longer study was required to assess cognitive improvements. Currently concerns remain regarding the effects of selective GSK-3 inhibition. However, lithium, a known inhibitor of GSK3, has been used to treat bipolar disorder for over 50 years.

Although the precise mechanisms of action of lithium remain the subject of debate there is evidence that at least some of its actions are mediated by inhibition of GSK3. The IC₅₀ (50% inhibition constant) for direct GSK3 inhibition *in vitro* (approximately 0.5 mmol/L) lies at the lower end of the therapeutic range of lithium (0.4–1.0 mmol/L), suggesting that the doses used in clinical practice generate pharmacologically relevant GSK3 inhibition. In addition lithium (unlike more specific GSK3 inhibitors) also reduces GSK3 gene transcription and can induce upstream pathways that negatively regulate GSK3 (at least in rodents and human cells). Therefore, inhibition of GSK3 by lithium *in vivo* could well be greater than that presumed from *in vitro* assessed IC₅₀ values. Clearly the actual dose–response association between lithium and GSK3 activity in humans requires robust experimental evaluation, but the preclinical evidence suggests that lithium reduces activity of an enzyme proposed as a therapeutic target in Alzheimer's disease. This raises two important questions: (a) does lithium treatment have any therapeutic efficacy in Alzheimer's disease, and (b) if therapeutic efficacy is related to GSK3 inhibition would more selective GSK3 inhibitors be worth pursuing as novel Alzheimer's disease therapeutics?

Lithium and dementia

Lithium administration to rodent models of Alzheimer's disease reduces generation of Alzheimer's disease pathology and cognitive decline. Of course, there is serious concern over the translation of

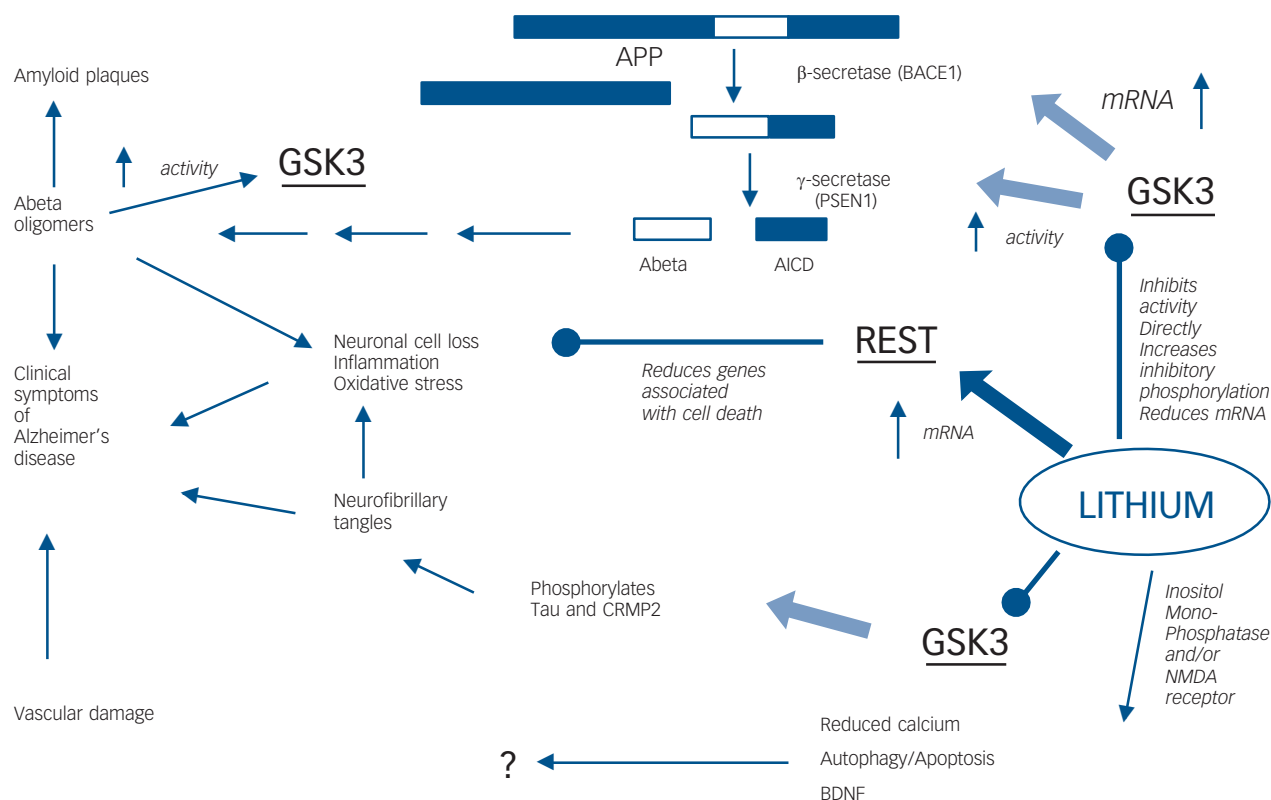


Fig. 1 Proposed mechanistic links between lithium and symptoms of Alzheimer's disease that could explain the observed protection from dementia development.

High glycogen synthase kinase-3 (GSK3) and repressor element 1-silencing transcription factor (REST) are found in Alzheimer's disease brain tissue. Increased GSK3 enhances both β -secretase (BACE1) and presenilin-1 (PSEN-1) activity promoting amyloid beta (abeta) generation, and increases in amyloid beta are linked to high GSK3, suggesting a cycle of worsening pathology. GSK3 is also a tau and collapsin response mediator protein 2 (CRMP2) kinase, and hyperphosphorylated tau and CRMP2 are found in the brains of people with Alzheimer's disease and may contribute to tangle formation. REST is a neuroprotective transcriptional regulator. Lithium reduces GSK3 activity (potentially by direct inhibition, enhancing inhibitory regulation and reducing GSK3b gene transcription) and induces REST production. In addition it may have other beneficial actions through its regulation of inositol monophosphatase (IMP) and *N*-methyl-D-aspartate (NMDA) receptors. APP, amyloid precursor protein; AICD, APP intracellular C-terminal domain; BDNF, brain-derived neurotrophic factor; mRNA, messenger ribonucleic acid.

findings in rodents to humans. However, lithium increases both grey matter and *N*-acetyl-aspartate levels in human brain, supportive of a neuroprotective action of lithium in humans. The importance of GSK3 inhibition in these actions of lithium requires validation, as there are other targets of lithium proposed to be neuroprotective. Lithium regulates calcium levels through inositol monophosphatase and/or *N*-methyl-D-aspartate (NMDA) receptors, and regulates autophagy, apoptosis and mitochondrial function. Lithium increases serum brain-derived neurotrophic factor (BDNF) levels in Alzheimer's patients⁶ and induces the repressor element 1-silencing transcription factor (REST), a protein known to decline in Alzheimer's disease (and in mild cognitive impairment).⁷ REST induces genes that antagonise cell death and is thus neuroprotective⁷ (Fig. 1). Taken together this indicates that lithium has multiple potential mechanisms that would antagonise processes associated with dementia.

The belief that lithium has severe toxicity in humans has limited its investigation in trials for dementia protection almost exclusively to people with bipolar disorder. In truth, lithium is an exceptionally well-studied agent with a predictable side-effect profile and when clinically relevant blood concentrations are achieved it is reasonably well-tolerated. In contrast, accumulation of lithium results in serious side-effects and to avoid toxicity serum levels are routinely monitored in clinical practice and kept within the therapeutic range of 0.4–1.0 mmol/L. Therefore studies in appropriate populations for dementia research are feasible, although most studies have examined dementia in patients with

bipolar disorder. Two initial observational studies generated opposite conclusions, one study suggesting that lithium promoted dementia development in patients with bipolar disorder, the second finding protection with lithium.^{8,9} Subsequently two Danish studies indicated a major reduction in dementia associated with long-term lithium use. More recently a pilot study of lithium treatment in mild cognitive impairment indicated a trend towards cognitive benefit (and 91% tolerability) but this trial was too short to investigate conversion to dementia.¹⁰ Similarly, 10-week administration of lithium in people with mild to moderate Alzheimer's disease provided no protection from cognitive decline, but this study did report reduced phosphorylation of cerebrospinal fluid tau with lithium.¹¹ These studies support the notion that lithium can be tolerated in patients with mild cognitive impairment or Alzheimer's disease, and it can improve pathological markers, but like most interventions for dementia more chronic treatment will be required to assess effects on symptoms, and these may only be apparent in earlier stages of the disease.

In support of this, a small randomised, controlled trial found that relatively low-dose (300 μ g daily) lithium for 15 months reduced cognitive decline in Alzheimer's disease patients,¹² and now, the largest retrospective epidemiological analysis of dementia diagnosis in older adults treated with lithium ever conducted ($n > 40\,000$) has provided the most convincing evidence to date that lithium protects against progression to dementia.¹³ Continuous lithium treatment for 10–12 months

reduced the development of clinical dementia (all forms) when compared with two groups of patients with bipolar disorder receiving shorter, intermittent lithium or no lithium (anti-convulsants). Although such studies are fraught with confounding issues, the association between continuous lithium use and lower risk of dementia held true through adjustment for over 20 covariates. This robust and extensive study provides real optimism that there is a cheap, ready-to-use drug available that could prevent or slow down the development of dementia.

An opportunity too good to pass up?

Should lithium be fast-tracked to clinical trials? The lack of progress in developing therapeutics for dementia would suggest yes, although many key questions remain. Will lithium have efficacy in all groups at high risk of developing dementia (for example mild cognitive impairment, diabetes)? What is the most logical/appropriate stage of disease development to target, and what dose and for how long to treat? Possibly the key question though is will lithium toxicity ever be accepted as manageable?

The toxicity and efficacy issues would benefit greatly from robust preclinical data on mechanism. At present it is not clear if inhibition of GSK3 is the sole or even major mechanism for the beneficial actions of lithium on dementia in humans. Data in mice have suggested that lithium actions on behaviour are similar to deletion of one of the four GSK3 alleles, and also the response to structurally distinct GSK3 inhibitors.¹⁴ This supports GSK3 being the key lithium target for its neuronal actions and that complete inhibition of GSK3 is not crucial to these actions. Indeed, we hypothesise that a lower dose of lithium than that used in bipolar disorder would have efficacy in dementia. In order to minimise toxicity concerns, the lithium dose required to reduce GSK3 activity in patients with high GSK3 should be established. However, more accurate and robust biomarkers of GSK3 activity are required. The current approach of measuring one aspect of GSK3 post-translational modification does not provide a true assessment of the cellular activity of this enzyme. Robust biomarkers of GSK3 activity would allow lithium efficacy and its association with GSK3 reduction to be assessed in a prospective randomised case-control study. Harnessing mechanistic information on any benefits of lithium action would clearly enhance opportunities for novel interventions. This data is a prerequisite to fully determine the potential of more selective inhibitors of GSK3, and the therapeutic window for such agents. Future trials, even those employing low blood concentrations of lithium, will have to address concerns regarding potential side-effects including lithium toxicity. Regular blood tests for renal function and lithium concentration will improve safety. Previous studies in people with bipolar disorder have suggested that lithium has an adverse impact on some measures of cognition, including attention, although studies have yielded conflicting results. Therefore careful monitoring of participants for adverse effects on cognition is advisable. The data available would suggest that clinical trials

should focus on the prodromal phase of Alzheimer's disease, mild cognitive impairment, since this phase is more likely to be amenable to manipulation of the proposed lithium targets than established disease.

In summary, new clinical data suggest lithium has the potential to prevent dementia development. With little evidence of novel therapeutics on the horizon for the millions of people at risk of dementia it would seem negligent not to investigate lithium in dementia prevention more thoroughly.

Calum Sutherland, BSc, PhD, Division of Cardiovascular and Diabetes Medicine, Ninewells Medical School, Dundee, Scotland; **Ashleigh C. Duthie**, MRCPsych, MSc, Susan Carnegie Centre, Stracathro Hospital, near Brechin, Scotland

Correspondence: Calum Sutherland, Division of Cardiovascular and Diabetes Medicine, Ninewells Medical School, Dundee, DD1 9SY, Scotland. Email: c.d.sutherland@dundee.ac.uk

First received 23 Oct 2014, final revision 10 Dec 2014, accepted 17 Feb 2015

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