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Calcium dysregulation, and lithium treatment to forestall Alzheimer's disease – a merging of hypotheses☆

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ABSTRACT

Intracellular Ca^{2+} concentrations are tightly regulated, and elevated levels sustained over periods of time can cause cellular deterioration. The putative role of dysregulated intracellular Ca^{2+} in Alzheimer's disease had led to the hypothesis that controlling intracellular Ca^{2+} may forestall cognitive decline. Lithium has been shown to reduce intracellular Ca^{2+} concentrations. Two well-characterized neuronal targets of lithium that may affect intracellular Ca^{2+} levels are N-methyl-D-aspartate (NMDA) receptors and inositol monophosphatase (IMP). Results from a recent single-center placebo-controlled randomized trial suggest that long-term lithium treatment at subtherapeutic doses may have the potential to delay the progression of disease, and observational studies have shown that lithium reduces the prevalence of dementia in subjects with bipolar disorder on long-term lithium therapy. I am advancing the hypothesis that lithium may protect against cognitive decline by stabilizing intracellular Ca^{2+} through a dual, synergistic mechanism of targeting both extracellular and intracellular sites, via antagonizing NMDA-receptors and inhibiting IMP. Insights derived from this hypothesis could lead to an improved understanding of the molecular pathology of Alzheimer's disease, and have implications on the evaluation and use of therapeutics that alter intracellular Ca^{2+} levels.

1. Introduction

Alzheimer's disease is a progressive neurodegenerative illness, and without new interventions, the global prevalence is predicted to increase from 26.6 million people in 2006 to over 100 million by 2050 [1]. A large majority of cases are sporadic, affecting adults over age 65. Less common variants, including cases of non-sporadic Familial Alzheimer's Disease (FAD), typically have an onset before age 60, and result from mutations in genes that encode Amyloid Precursor Protein (APP), Presenilin 1, or Presenilin 2 [2] (for a review of Alzheimer's disease, see Querfurth and LaFerla [30]).

An emerging body of clinical evidence suggests that lithium may have neuroprotective effects. Results from observational studies involving subjects with bipolar disorder on lithium therapy have shown that long-term lithium treatment is associated with a reduced prevalence of dementia [3,4]. In interpreting these results, it is important to note that dementia rates are higher in patients with affective disorders [5–8], and the dementia rates observed in patients with bipolar disorder on long-term lithium therapy are approximately equal to the dementia rates found in the general population [3,4]. The therapeutic serum range of lithium for the long-term control of bipolar disorder in healthy adults is 0.6–1.2 mEq/L [9]. Data from a recent single-center placebo-controlled randomized trial by Forlenza et al. (2011) involving subjects with amnesic mild cognitive impairments (MCI) ($n = 45$) suggests that long-term lithium therapy at subtherapeutic levels (serum levels 0.25–0.5 mEq/L) may protect against Alzheimer's disease [10]. This 12-month study found that subjects treated with lithium maintained stable cognitive performance and had lower rates of progression to Alzheimer's disease compared to subjects on placebo (the results were not statistically significant). The low-dose lithium regimen was selected to improve long-term tolerance in older adults. The candidate mechanism of lithium cited by the authors in the above referenced clinical and observational studies is the inhibition of glycogen synthesis kinase-3 (GSK-3) [3,4,10]. GSK-3 is a family of enzymes implicated in the phosphorylation of tau [11,12].

Experimental evidence from in vitro studies has shown that lithium can antagonize or inhibit multiple targets [13]. This has complicated efforts to elucidate the in vivo pharmacodynamic

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activity of lithium. The targeting of multiple substrates by lithium may potentially be the basis for how lithium confers clinical benefits.

The calcium hypothesis of Alzheimer's disease proposes that chronically elevated concentrations of intracellular Ca^{2+} are an early, or a proximal cause, of disease [14–16]. NMDA-receptor overstimulation [17,18], and excessive inositol triphosphate (IP3) mediated Ca^{2+} efflux from the endoplasmic reticulum (ER) [15,19,20], are two of the proposed mechanisms implicated in neuronal Ca^{2+} dysregulation, and in the pathogenesis of Alzheimer's disease (for discussion of the candidate mechanisms that may contribute to Ca^{2+} dysregulation in aging and in neurodegenerative disease, see Bezprozvanny and Mattson [15]; Stutzmann [19]; Foskett [20]. Lithium has been shown to reduce intracellular Ca^{2+} levels at the therapeutically relevant concentration of 1.0 mEq/L [21]. The binding of lithium to NMDA-receptors and to IMP can potentially abrogate Ca^{2+} perturbations by antagonizing extracellular Ca^{2+} influx through NMDA-receptors, and reducing IP3 mediated Ca^{2+} efflux from ER stores by inhibiting the IMP/inositol signaling pathway. NMDA-receptor antagonism and IMP inhibition have been well-characterized at therapeutically relevant lithium concentrations [22–25].

There is little direct evidence that GSK-3 activity is elevated in Alzheimer's disease [26,27], and in vitro experiments measuring GSK-3 inhibition by lithium have typically utilized supratherapeutic dose ranges [28,29]. The current body of evidence suggests that any effect of lithium on GSK-3 is minor in comparison to the effect of lithium on intracellular Ca^{2+}. Rather than targeting GSK-3, I am predicting that lithium may forestall Alzheimer's disease by stabilizing intracellular Ca^{2+} via a dual, synergistic mechanism of antagonizing NMDA-receptors and inhibiting IMP.

2. Alzheimer's disease

The histopathological features of Alzheimer's disease include beta-amyloid peptide (Aβ) aggregates, neurofibrillary tangles (NFTs); and the loss of synapses, white matter, and neurons [30–33]. Aβ is principally a 40 or 42 amino acid peptide cleaved from APP, a larger transmembrane protein, by a two step process that involves enzymatic cleavage by β-secretase and then γ-secretase [15]. NFTs are hyperphosphorylated aggregates of the microtubular associated protein tau [30–32]. Evidence that Aβ production and aggregation precedes and promotes tau production and aggregation has led to the formulation of the amyloid cascade hypothesis [34–39], but the precise order of events leading to Alzheimer's disease has not been definitely elucidated [30], and the progression of pathology has remained unsolved [32]. Candidate subcellular sites where it is speculated that APP is cleaved into Aβ includes the ER/Golgi system – where APP undergoes post-translational processing as part of the secretory pathway, and in the endosomal/lysosomal system – where APP is re-internalized from the cell surface [40–43]. NFT aggregation tends to manifest during the advanced stages of Alzheimer's disease in the cell body and in the dendritic compartment of pyramidal neurons [32]. An important function of neurons commonly affected by Alzheimer's disease pathology is memory consolidation, a function mediated by transient increases in cytosolic Ca^{2+}.

3. LTP, LTD, and synaptic plasticity

In 1894, Santiago Ramón y Cajal proposed that memory and learning are mediated by the growth of synaptic connections [44], a concept expanded upon in the 1940's by Jerzy Konorski and Donald Hebb, and named synaptic plasticity [45,46]. As a framework developed for understanding memory storage, progress was made in elucidating the molecular events within neurons that mediate synaptic plasticity.

Long-term potentiation (LTP), which is associated with synaptic strengthening and synaptic growth, is mediated by the influx of Ca^{2+} into the cytosol of post-synaptic neurons [47–52]. Within neurons, the resting $[Ca^{2+}]_i$ is approximately 100 nM, a level that can rise to 500–1000 nM during neuronal activation [53]. This transient rise in Ca^{2+} results in the activation of kinases associated with LTP, leading to transcription, translation, and neuronal remodeling [50,51]. LTP has been divided into two phases. The early-phase LTP, lasting approximately 60 min, and the late-phase LTP, which is the protein synthesis dependent component of LTP [50]. Plasma membrane trafficking, which involves the synthesis, delivery, and re-internalization of membranes and membrane proteins (including APP), has been described in the context of post-synaptic processes associated with LTP and synaptic remodeling [52,54–58].

During stimulation, Ca^{2+} flows into the cytosol of post-synaptic neurons from two principal sources: the extracellular space, and the ER [53,59]. Extracellular Ca^{2+} can enter through cell surface channels including voltage dependant channels (e.g., L type voltage-gated calcium channels) and receptor dependant channels (e.g., NMDA-receptor channels) [53]. Ca^{2+} from the ER flows principally through ryanodine channels and IP3 channels [53,59].

There are at least four mechanisms that depend either directly or indirectly on cell energy to remove Ca^{2+} from the cytosol to maintain homeostasis. Plasma Membrane Calcium ATPase (PMCA) pumps; Sarco-Endoplasmic Reticulum Calcium ATPase (SERCA) pumps that are involved in sequestering calcium into the ER; Na^+/Ca^{2+} antiporter exchange driven by the Na^+ gradient that is maintained through the operation of the Na^+/K^+ ATPase pumps; and Ca^{2+} uptake by the mitochondria driven by mitochondrial membrane potentials [60].

Long-term depression (LTD), which is associated with synaptic weakening, is also mediated by post-synaptic Ca^{2+} signaling [50,52]. The amplitude and duration of cytosolic Ca^{2+} transients that mediate LTD have been described as lower and more prolonged in comparison to LTP [61–63]. Bezprozvanny and Hiesinger [52] proposed that the nature of cytosolic Ca^{2+} signaling described with LTD might be similar in character to the intraneuronal milieu that predominates in aging neurons and in Alzheimer's disease (see Bezprozvanny and Hiesinger [52], for discussion of Ca^{2+} signaling, membrane trafficking, and synaptic maintenance in cognitive decline).

4. The calcium dysregulation hypothesis of Alzheimer's disease

During the past three decades, dysregulated intracellular Ca^{2+} has been linked to aging, and to Alzheimer's disease [14–16] (for history – see the Annals of the New York Academy of Sciences, Volume 568–1989, Volume 747–1994). Increased intracellular Ca^{2+} concentrations have been observed in neurons from aging mice and rats [64–67], and in neurons from 3xTg-AD transgenic mice [68].

Presenilins (PSs) are integral membrane proteins that form part of the gamma secretase multimeric enzyme complex that cleaves of APP into Aβ; and PSs are located primarily in the ER, Golgi complex, and the plasma membrane [15]. Because the clinical and pathological features of FAD are similar to sporadic disease, FAD PS-mutations have been evaluated to characterize disease mechanisms – and excessive IP3 mediated Ca^{2+} efflux has been observed [15,19,20,69,70] (for review, see Stutzmann and Mattson [69]; Honarnejad and Herms [70]).

Briefly, some of the candidate mechanisms that describe how FAD PS-mutations may contribute to excessive IP3 mediated Ca^{2+}

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