Medical Hypotheses
Available online 20 January 2020, 109573
In Press, Journal Pre-proof

Reducing the progression of Alzheimer's disease in Down syndrome patients with micro-dose lithium

Garrick A. Priebe, Mark M. Kanzawa

Show more

https://doi.org/10.1016/j.mehy.2020.109573

Abstract

Alzheimer's disease (AD) is a pervasive and progressive neurodegenerative disorder characterized by a gradual decline in memory, leading to significant impairments in cognition, language, and social functioning. An early-onset variant of the disease is a substantial source of morbidity in individuals with trisomy 21, the main cause of Down syndrome (DS), with clinical evidence of the disease seen in roughly one-half of those 50 years and older. Current pharmacologic therapies are limited to a handful of medications that offer only modest improvement in cognition and overall functioning. There is growing consensus in the literature that lithium salts, well-established as efficacious in the treatment of select affective disorders, may also provide neuroprotection from the development and progression of AD by targeting multiple processes implicated in the disease. These include beta-amyloid production, tau hyperphosphorylation, mitochondrial dysfunction, oxidative stress, and neuroinflammation. While complex, inhibition of glycogen synthase kinase 3 (GSK-3) appears to be the primary mechanism by which lithium exerts its disease-modifying effects. Reduced rates of dementia have been described in bipolar patients chronically treated with lithium. Additionally, "micro-dose" lithium (300 micrograms daily in one study) demonstrated stabilization of cognitive decline in AD patients with mild cognitive impairment. With encouraging data suggesting that lithium confers a clinically significant benefit in AD by impeding accumulation of the aberrant proteins central to the putative pathogenesis, it follows to reason that a population with a genetic predisposition rooted in this

disease mechanism may benefit from it. After a thorough review of the literature and currently active clinical trials, no studies have looked at using lithium to slow or prevent the development of Alzheimer's disease in the Down syndrome population. Because those with DS have such reliably high rates of developing AD, many 20-30 years younger than those in the general population, they represent an exemplary subject population to investigate the effect that lithium has on progression to disease. Furthermore, the specific factors that make those with Down syndrome prone to developing AD, including enhanced ability to synthesize beta-amyloid, mitochondrial dysfunction, and elevated oxidative stress, correlate quite well with the model by which lithium is thought to disrupt Alzheimer's pathogenesis, making the DS population ideally suited to study this intervention. Demonstrating reduced progression of Alzheimer's pathology with micro-dose lithium in those with trisomy 21 could function to reinforce our current understanding of the pathogenetic mechanism underlying early-onset AD, and ultimately, establish a preventative treatment for the disease.

Recommended articles Citing articles (0)

View full text