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Nifedipine: Can this Calcium Channel Blocker be Used "Off Label" to Inhibit the Development and Symptoms of Alzheimer's Disease and Related Beta-Amyloid-Producing Syndromes?

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Abstract

Alzheimer's disease needs no formal introduction. Losing a lifetime of information, experience, and memories is an undesirable and daunting end to a person's life, affecting not only the person but also their family and friends. The cost to the individuals involved and society as a whole is onerous. Currently, no medications or successful treatment are available to stop the progression of this disease; there are only ways to prolong life and put off the inevitable neural degeneration and cognitive dysfunction. The genetic component of Alzheimer's is at the research forefront, and the relationship between the pathways of similar amyloid-related genetic conditions, such as Down syndrome, may have a commonality. It is considering these pathways where "off label" use of a common medication, Nifedipine, may offer improved outcomes in the treatment or amelioration of Alzheimer's-related symptoms in halting the progression of this most pernicious and dreadful disease.

Keywords: *Alzheimer's Disease; Amyloid; Beta-Amyloid; Down Syndrome; Nifedipine, Presenilin*

Abbreviations

AD: Alzheimer's Disease; ApoE: Apolipoprotein E; APP: Amyloid Precursor Protein; BBB: Blood-Brain Barrier; BA: Beta Amyloid; CCB: Calcium Channel Blocker; CSP: Calcium Signaling Pathway; FAD: Flavin Adenine Dinucleotide; LTD: Long-Term Depression; LTP: Long-Term Potentiation; NMDA: *N*-Methyl-D-Aspartate; NMDAR: *N*-Methyl-D-Aspartate Receptor; PRES1: Presenilin 1; PRES2: Presenilin 2; RYR: Ryanodine Receptor

Introduction

Alzheimer's disease (AD) is commonly known and has become a plague to humankind; particularly, those persons 65 years of age and above. The progression of AD results in the loss of lifelong personal and family memories, accumulated knowledge, and educational and work experience [1]. It impacts the affected person's loved ones like no other disease, and the thought of someday being afflicted by AD frightens most rational and sensitive human beings, especially those with a genetic predisposition to AD and, currently, no hope for prevention or cure. The cost to the individuals involved and society as a whole is enormous [2]. According to the NIH National Institute of Aging Alzheimer's Disease Fact Sheet:

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and, eventually, the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear in their mid-60s. Estimates vary, but experts suggest that more than 5.5 million Americans, most of them age 65 or older, may have dementia caused by Alzheimer's. "Alzheimer's disease is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people. Alzheimer's is the most common cause of dementia among older adults. Dementia is the loss of cognitive functioning-thinking, remembering, and reasoning-and behavioral abilities to such an extent that it interferes with a person's daily life and activities. Dementia ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of daily living. [3]

Research suggests that the main component of this disease process is beta-amyloid (BA) production. Extracellular BA accumulation is responsible for senile plaques; while intracellular BA causes hyperphosphorylation of tau proteins, adversely affecting mitochondrial function and triggers the calcium channel pathway.

Discussion

Dealing with beta-amyloid plaque formation

The current pharmacological protocol for addressing AD is varied and with some disappointing results [4]. One approach is to inhibit anticholinesterase by using tacrine, galantamine, donepezil, physostigmine, or rivastigmine. Another approach is to antagonize the N-methyl-D-aspartate receptor (NMDAR) by using memantine. Yet, another approach is to bind the BA peptides and prevent BA aggregation by using solanezumab, bapineuzumab, or gantenerumab. A final approach was to suppress BA formation [5]—through modulation of gamma-secretase—by using tarenflurbil* or through inhibition of gamma-secretase by using semagacestat*, begacestat, or avagacestat (Table 1) [*Note. These medicines are no longer used due to failed trials].

Method of Action	Current Drug of Choice
Anticholinesterase Inhibitor	Tacrine
	Galantamine
	Donepezil
	Physostigmine
	Rivastigmine
NMDA receptor agonists	Memantine
BA suppression Gamma secretase inhibition	Tarenflurbil Semagacestat Begacestat Avagostat
BA aggregation prevention	Solanzumab Bapineuzumab Gantenerumab

Table 1: *Illustrating the "method of action" for particular drugs in the treatment of AD.*
Note: Mitchell G. Jomsky (2019).

Genes involved in AD via BA formation

To interrupt or halt BA formation is a logical, albeit superficial and symptomatic, approach, to the treatment of AD as there is a predisposing genetic component to BA production and formation. BA formation, and thus AD, persists despite the application of current treatment regimens [4].

Early-onset and late-onset AD have been associated with several genes: amyloid precursor protein (APP), apolipoprotein E (ApoE), presenilin 1 (PRES1), and presenilin 2 (PRES2). APP, PSEN1, and PRES2 have been observed in early-onset AD, while ApoE has a late onset association [6].

ApoE occurs as three possible isoforms that differ based on two amino acid residues (112 and 158): APOEε2, APOEε3, and APOEε4. APOEε3 is the most common ApoE isoform, occurring in approximately 72% of the population. Family-based methods initially identified a genetic linkage between AD in the region of chromosome 19, which contains the ApoE gene. APOEε4 increases the risk in familial and sporadic early- and late-onset AD; increasing the risk three-fold for heterozygous carriers and increasing the risk 8–10-fold for homozygous carriers. Also, APOEε4 has a dose-dependent effect on age at onset (Figure 1). Interestingly, APOEε2 decreases the risk for late-onset AD and delays the age of onset [6].

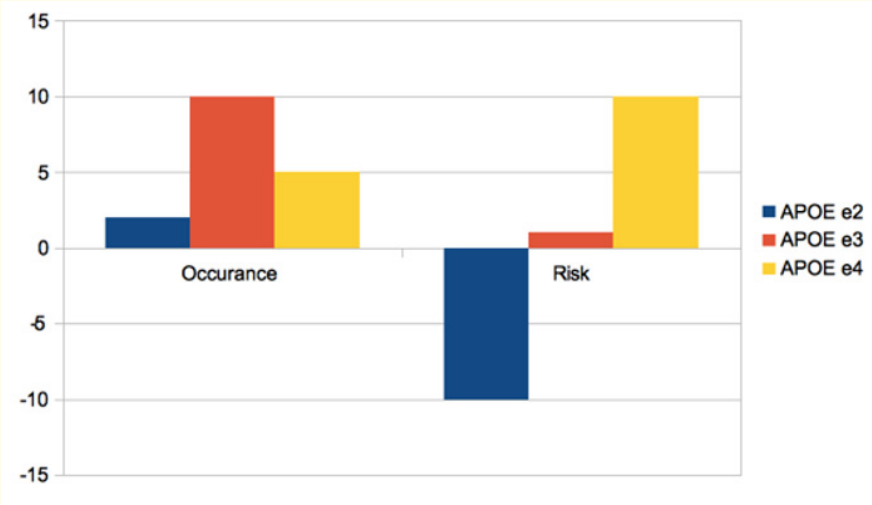

Figure 1: *Most common APOE genetic risks for Alzheimer's disease.*
Note: Mitchell G. Jomsky (2019).

According to Brzyska and Elbaum (2003): "Studies of apolipoprotein E (ApoE) neurotoxic effects in AD confirmed involvement of Ca^{2+}-mediated mechanisms" [7]. A person inherits a maternal and a paternal ApoE gene. Should either parent pass on one APOEe4 gene, the risk of that offspring having BA-associated dementia increases; while receiving homozygous alleles of APOEε4 significantly increase that risk. Moreover, the risk or delay of onset of Alzheimer's is reduced with either maternal or paternal contribution of the APOEε2 gene. Risk reduction or delay of onset decreases significantly when both APOEε2 genes are present [8]. Maternal and paternal APOEε3 alleles, whether homozygous or heterozygous, do not significantly change the outcome, as depicted in Figure 2.

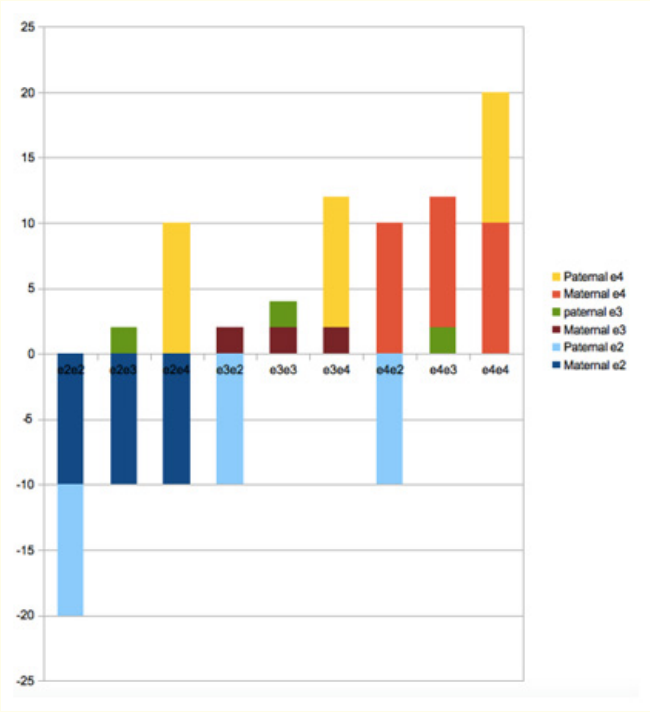

Figure 2: *Most common APOE genetic risks for Alzheimer's disease.*
Note: Mitchell G. Jomsky (2019).

Genes associated with early-onset AD

Three other genes are associated with early-onset AD. If a person inherits a single mutated gene from either parent, they will likely experience Alzheimer's symptoms before age 65. The genes involved are APP, PRES1, and PRES2. Mutations of these genes cause the production of excessive amounts of a toxic protein fragment, termed amyloid-beta peptide (β-amyloid peptide). As these β-amyloid peptide fragments stick together and collect in the brain as amyloid plaques, the tau protein malfunctions. Then, the tau protein particles stick together and form neurofibrillary tangles, causing brain cells to die, resulting in the signs and symptoms of AD [9].

Calcium signal pathway

There are well-documented connections between cell death and calcium. It is the death of the brain cells—by the various protein particles listed above—that trigger the calcium signal pathway (CSP).

Recent studies in AD models have identified marked dysregulations in calcium signaling and related downstream pathways [10], which occurs long before the diagnostic histopathological or cognitive changes are noticed. Under normal conditions, intracellular calcium signals are coupled to effectors that maintain a healthy physiological state. Consequently, sustained upregulation of calcium may have pathophysiological consequences. According to Stutzman (2007): "Indeed, the current body of literature indicates that increased calcium levels are functionally linked to the major features and risk factors of AD: ApoE4 expression, presenilin and APP mutations, beta-amyloid plaques, hyperphosphorylation of tau, apoptosis, and synaptic dysfunction. In turn, the histopathological features of AD, once

formed, are capable of further increasing calcium levels, leading to a rapid feed-forward acceleration once the disease process has taken hold" [11]. According to the NIH National Institute of Aging Alzheimer's Disease Genetics Fact Sheet: "Early-onset FAD (flavin adenine dinucleotide) is caused by any one of a number of different single-gene mutations on chromosomes 21, 14, and 1. Each of these mutations cause abnormal proteins to be formed. Mutations on chromosome 21 cause [sic] the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2 [11]".

Each of these mutations plays a role in the breakdown of APP, a protein which precise function is not yet fully understood. This breakdown is part of a process that generates harmful forms of amyloid plaques, a hallmark of the disease.

Ryanodine receptor defects and calcium-signaling mechanisms in AD

Memory is lost in an Alzheimer's-afflicted patient; thus, preserving memory is a goal in AD prevention, amelioration, or cure. In essence, memory is a series of neural synaptic connections. NMDARs are increased in strong synaptic connections, long-term potentiation (LTP), while decreased in weaker synaptic connections, long-term depression (LTD). LTP and LTD are long-lasting changes in synaptic strength and are factors in the encoding of memory. The induction of LTP and LTD share a common trigger: an increase in intracellular Ca^{2+} [12]. In LTP, brief high-frequency afferent activity leads to a long-lasting increase in the strength of synaptic transmission; whereas, prolonged low-frequency afferent activity results in a persistent reduction in synaptic strength. Both processes (LTP and LTD) are triggered by an increase in the level of postsynaptic intracellular calcium concentration [13].

Cellular calcium concentrations are regulated by ryanodine receptors (RYRs) in the endoplasmic reticulum. The integrity of the RYRs in AD plays a critical role in the regulation of calcium release from the endoplasmic reticulum in the brain; the impairment of this regulation is thought to contribute to the pathogenesis of AD [14]. Due to the resultant Ca^{2+}-signaling abnormalities, a balance in the activities of Ca^{2+} calmodulin-dependent kinase II and Ca^{2+}-dependent phosphatase calcineurin is altered at the synapse, shifting the balance between LTP and LTD synaptic mechanisms in favor of the LTD mechanism. As a result, synapses are weakened and eliminated in AD brains, causing memory loss [15].

Summary of genetic factors

Based on the above information, genetics plays a role in the inheritance of AD and the onset of dementia. (As there is a connection to chromosome 21 [16], children with Down syndrome might be included in the discussion of early-onset AD.) There are many other "self-inflicted scenarios" that can amplify the risk of AD onset. For example, boxers and football players can suffer from forms of dementia [17], after a history of repetitive concussive head traumas—whether genetically-predisposed or not. Also, poor nutrition can impair cerebral vascular health. The resultant deposition of calcium and plaques can obstruct arteries, which compromises the delivery of oxygen and nutrition to the brain tissue.

For now, it seems that a genetic-based treatment or cure for AD is not on the research horizon. Thus, a more symptomatic approach to AD may be a more pragmatic short- to mid-term solution.

Alternate pathways in the suppression of BA and the treatment of AD

A simple, in theory, approach in coping with AD development may be to increase oxygen to the brain while decreasing the detrimental effects of BA. Besides the tau hyperphosphorylation and neurofibrillary tangle (NFT) formation [18], another consideration is the triggering of the CSP. The CSP increases calmodulin, which is the calcium carrying protein that causes the influx of calcium in the brain. This influx of calcium is responsible for long-term depression and memory loss and or learning problems. Thus, blocking of the calcium channels may serve to decrease the more debilitating symptoms of AD or, at least, delay the onset of dementia. As reported by Wang

and Epstein (2011): "In a study performed recently in China, patients on calcium CCB medications showed some resolution of AD-type symptoms, which may support the preceding supposition" [19]. According to Wang and Epstein (2011):

> In the Syst-Eur study, active antihypertensive treatment was started with a calcium channel blocker, nitrendipine. In that study, Professor Fagard, from Paris, and Jan Staessen, from Leuven, Belgium, observed a very big reduction in the incidence of dementia. In the beginning of this study, they planned to do a sub-study looking at prevention of vascular dementia, but finally they observed a reduction in the risk of all dementias, including degenerative dementia, Alzheimer disease, and also vascular dementia. This means that if you use a calcium channel blocker, an antihypertensive drug, you may not only prevent stroke and cardiovascular events, you may also prevent dementia. [19]

Assuming CCBs may positively influence dementia, what would be the best CCB drug(s) to use in a population of early-onset and late-onset AD patients (and Down syndrome patients)?

When choosing CCB medications for ischemic heart disease [20], a balance needs to be struck between oxygen demand versus oxygen supply. Researchers may be advised to focus on agents that increase oxygen supply through vasodilation while preventing changes to chronotropy and inotropy of the heart, in order for patients to tolerate long-term usage to prevent and or treat Alzheimer's (and Down Syndrome). These CCBs need to cross the blood-brain barrier (BBB) so calcium uptake can be blocked, while cerebral vasodilation increases oxygen supply to the targeted tissues. If a drug can successfully cause reduced calcium uptake in the affected and targeted region, while increasing oxygen perfusion, perhaps the detrimental effects of BA can be diminished or eliminated?

The drug, nifedipine, may be able to do just that. Nifedipine, given intravenously, increases forearm blood flow with little effect on venous pooling [21]; this indicates a selective dilation of arterial resistance vessels. The decrease in arterial blood pressure elicits sympathetic reflexes with resulting tachycardia and positive inotropy. Also, nifedipine displays direct adverse inotropic effects in vitro. However, nifedipine relaxes the vascular smooth muscle [22] at significantly lower concentrations than those required for noticeable direct effects on the heart. Thus, arteriolar resistance and blood pressure are lowered, contractility and segmental ventricular function are improved, and heart rate and cardiac output are increased modestly. After oral administration of nifedipine, arterial dilation increases peripheral blood flow; venous tone does not change [23].

Conclusion

Can prophylactic oral administration of nifedipine be a safe and effective "protector against dementia" for adults genetically predisposed to AD (and for children with Down syndrome)? Can the risks of the administration of CCBs over the long-term be outweighed by any beneficial effects on cognitive longevity? The prophylactic oral administration of nifedipine for the prevention or deterrence of AD symptoms seems worth looking into in more formal research. Clinical trials and prospective studies would be needed in order to determine the efficacy of this novel and "off label" use of CCBs to deter or, perhaps, stop the symptoms of Alzheimer's and related dementias.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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