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Hypothesis

Aniracetam: An Evidence-Based Model for Preventing the Accumulation of Amyloid-β Plaques in Alzheimer's Disease

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Abstract. Alzheimer's disease is the leading cause of dementia in the world. It affects 6 million people in the United States and 50 million people worldwide. Alzheimer's disease is characterized by the accumulation of amyloid-β plaques (Aβ), an increase in tau protein neurofibrillary tangles, and a loss of synapses. Since the 1990s, removing and reducing Aβ has been the focus of Alzheimer's treatment and prevention research. The accumulation of Aβ can lead to oxidative stress, inflammation, neurotoxicity, and eventually apoptosis. These insults impair signaling systems in the brain, potentially leading to memory loss and cognitive decline. Aniracetam is a safe, effective, cognitive-enhancing drug that improves memory in both human and animal studies. Aniracetam may prevent the production and accumulation of Aβ by increasing α-secretase activity through two distinct pathways: 1) increasing brain derived neurotrophic factor expression and 2) positively modulating metabotropic glutamate receptors. This is the first paper to propose an evidence-based model for aniracetam reducing the accumulation and production of Aβ.

Keywords: Aging, α-secretase, Alzheimer's disease, amyloid plaques, aniracetam, BDNF, cognition, dementia, neurobiology, pharmacology

Aniracetam is a known cognitive enhancer whose pharmacological mechanisms are not fully understood. The main metabolites of aniracetam are N-anisoyl-γ-aminobutyric acid (N-anisoyl-GABA), 2-pyrrolidinone and anisic acid [1]. Aniracetam modulates metabotropic glutamate receptors (mGluRs) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive glutamate receptors, and it increases cholinergic activity in the hippocampus, prefrontal cortex, and striatum [2]. It also protects against glutamate excitotoxicity [3]. Aniracetam, in combination with AMPA, increases brain-derived neurotrophic factor (BDNF) [4], an important trophic factor in the brain that supports healthy memory, neurogenesis, and synaptogenesis [5]. A recent study from 2023 found that aniracetam, when combined with perampanel, reduces inflammation, and increases BDNF [6]. Research in humans and animals finds aniracetam has excellent safety, tolerability, and few drug interactions, making it an ideal candidate for the prevention and treatment of Alzheimer's disease (AD) [1, 7].

ALPHA-SECRETASE

The majority of AD drugs have attempted to treat and prevent AD by reducing Aβ [8]. Many of these drugs have attempted to inhibit β-secretase as a means of reducing Aβ production [9]. Unfortunately,

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clinical trials using this approach have failed. Also, because β-secretase and γ-secretases both have multiple substrates other than amyloid-β protein precursor (AβPP), they are not ideal for AD treatment.

Targeting α-secretase activity is attractive therapeutically for AD because increasing α-secretase cleavage of AβPP has multiple positive effects regarding AD pathology [10]. First, cleaving AβPP with α-secretase prevents Aβ liberation. Second, α-secretase cleavage of AβPP produces sAβPPα, which is known to be neuroprotective [11]. Specifically, sAβPPα plays important roles in neuronal plasticity and survival: 1) it protects hippocampal neurons against excitotoxicity, 2) it protects neurons from Aβ toxicity, and 3) it protects neurons from hypoglycemic damage [12]. Third, there may be other neuroprotective downstream effects of upregulating α-secretase activity. For example, α-secretase is involved in the regulation of pro-inflammatory cytokines [13], and increasing α-secretase may reduce inflammation. Inflammation is a well-established risk factor for AD [14]. Because of the multiple neuroprotective effects of α-secretase, enhancing α-secretase activation is likely to help prevent AD [15].

It is important to note that α-secretase has multiple downstream substrates, and little is known about the signaling pathways that may stimulate α-secretase cleavage of AβPP [16].

Evidence suggests that aniracetam has the potential to increase α-secretase activity, thereby reducing Aβ production, via two distinct pathways: first, by increasing activity of BDNF, and second, by positively modulating metabotropic glutamate receptors (mGluRs). Both BDNF and positive modulation of mGluRs increase α-secretase activity and decrease Aβ [17–19].

AMYLOID-β PLAQUES

Excess Aβ is believed to be a significant contributor to the dysfunction that occurs in AD [20, 21]. Accumulation of Aβ damages neurons and synapses and often contributes to neuroinflammation [22, 23]. Specifically, Aβ can lead to oxidative stress, inflammation, neurotoxicity, and eventually apoptosis. These insults impair signaling systems in the brain, potentially leading to memory loss and cognitive decline [24, 25]. Aniracetam, a known nootropic and cognitive enhancer [1, 2, 26], has the potential to reduce Aβ by facilitating the non-amyloidogenic processing of AβPP by elevating α-secretase activity via increasing BDNF and modulating mGluRs.

Aβ is a 39 to 43 amino acid peptide derived from AβPP [27]. There are three known proteases that cleave AβPP: α-, β-, and γ-secretases. Aβ is created when AβPP is cleaved by β-secretase and γ-secretase [23]. When AβPP is cleaved at the beta, gamma, and caspase sites, the result is four peptides: sAβPPβ (soluble AβPP cleaved at the beta site), Aβ, Jcasp (the juxtamembrane peptide cleaved at the caspase site) and C31 (the final 31 amino acids of the protein) [28]. When AβPP is cleaved at the alpha site by α-secretase, the result is sAβPPα (soluble AβPP cleaved at the α site) and αCTF (carboxyterminal fragment), an 83-amino acid chain which is subsequently cleaved by γ-secretase producing AβPP intracellular domain (AICD) and P3 peptides [23, 29]. sAβPPα has neuroprotective properties [11, 30]. When AβPP is cleaved by α-secretase, the production of Aβ is prevented. Therefore, increasing α-secretase activity is a potential pathway for decreasing Aβ production and accumulation, as well as increasing neuroprotective sAβPPα. Indeed, brains of AD patients are deficient in α-secretase [31], a deficiency in α-secretase levels accelerates AD pathology [29], and increasing α-secretase activity decreases Aβ production [32, 33].

It is important to note that simply reducing Aβ is not necessarily beneficial to cognition or helpful in the treatment of AD. Many drugs that reduce Aβ have failed to benefit humans in clinical trials. Since 2018, nine drugs that directly reduced Aβ have failed in Phase III trials [8]. And not all drugs that elevate α-secretase activity lower Aβ *in vivo* or show benefit in clinical trials (e.g., Etazolate) [34]. There remain many unknowns in the field of AD research and Aβ biochemistry.

BRAIN DERIVED NEUROTROPHIC FACTOR

Aniracetam increases BDNF [4]. Aniracetam is a well-established positive modulator of AMPA receptors [35–39], specifically in the dentate gyrus and CA1 regions of the hippocampus [40]. Aniracetam also slows the desensitization of AMPA receptors and enhances synaptic plasticity [36, 41]. Aniracetam administered with AMPA increases BDNF release and enhances BDNF gene expression; AMPA+aniracetam increased BDNF levels 1.5-fold, and levels remained elevated 6 hours later [4].

Researchers have suggested that part of the efficacy of aniracetam is its ability to increase BDNF, likely through mGluR modulation and increased cholinergic activity [2].

There is a strong and consistent association between increased BDNF and reduced levels of Aβ [17, 18]. A 2017 study by Mark Mattson and colleagues found that BDNF reduces Aβ by enhancing a pathway that involves α-secretase. Specifically, researchers treated *in vitro* cultured cells with BDNF and found a significant reduction in both $A\beta_{40}$ and $A\beta_{42}$, compared to control cultures. Researchers concluded that BDNF reduces Aβ levels by increasing α-secretase activity. Interestingly, and surprisingly, their research found that increasing α-secretase cleavage of APP by increasing BDNF did not directly increase ADAM10 [16].

A 2022 study found that BDNF helps regulate AβPP processing, likely through α-secretase [42]. Indeed, treating cultures with BDNF decreased $A\beta_{40}$ by 1.32-fold, decreased $A\beta_{42}$ levels by 2.15-fold, and increased sAβPPα by 1.50-fold [42]. Retinoic acid, a trophic metabolite of vitamin A, when combined with BDNF, increases sAβPPα production. Investigators concluded that this increase was due to retinoic acid and BDNF shifting AβPP processing in favor of the neuroprotective α-secretase pathway [43].

Conversely, low levels of BDNF are associated with an increased risk of AD. Indeed, those with AD have significantly lower levels of BDNF in their blood than healthy controls [44]. Some researchers speculate that BDNF may also decrease BACE1, which would decrease β-secretase cleavage and reduce Aβ liberation [43].

BDNF has other neuroprotective properties relevant to AD outside of its ability to elevate α-secretase activity and reduce Aβ. BDNF plays a crucial role in supporting the function and survival of neurons that deteriorate in the advanced stages of AD. BDNF protects against excitotoxicity, promotes regeneration of dendrites, and reduces apoptosis [45, 46]. A 2023 study found that BDNF helps protect both mitochondria and neurons. Specifically, BDNF was found to improve mitochondrial function, protect neurons from oxidative stress, and protect dendrites [47]. This is highly relevant to AD because oxidative stress and degeneration of mitochondrial function is associated with cognitive decline and increased risk of AD [48–50].

In the human brain, BDNF exists in two forms: the BDNF precursor, proBDNF, and mature BDNF. Existing research has demonstrated a significant reduction in both proBDNF and mature BDNF in the brain during the late stages of AD. Specifically, proBDNF is reduced by 30% in AD brains, and mature BDNF is reduced by 62% in AD brains. This decrease in BDNF is also associated with a decline in cognition [51].

By enhancing BDNF expression, aniracetam shows promise as a potential treatment for AD by reducing Aβ plaque, enhancing mitochondrial function, and supporting the survival of neurons.

METABOTROPIC GLUTAMATE RECEPTORS

L-glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS). mGluRs, which are classified as neuromodulatory receptors, offer a means for glutamate to regulate cell excitability and synaptic transmission through second messenger signaling pathways. Essentially, mGluRs modulate synaptic transmission and neuronal excitability throughout the CNS.

Glutamate and mGluRs may play an important role in AD [52]. Modulating mGluRs may help with AD in the following ways: 1) increase α-secretase activity and reduce Aβ formation, 2) protect against excitotoxicity, 3) reduce oxidative stress, and 4) enhance neuroplasticity [53, 54].

Aniracetam has the potential to reduce Aβ plaques by enhancing α-secretase activity by increasing mGluR activity. Aniracetam potentiates mGluR activity [2, 3, 55], and mGluR activation increases AβPP processing into non-amyloidogenic AβPPs in the hippocampus in rats [19]. Though other evidence suggests mGluRs stimulation may increase Aβ plaques [56].

The neurochemistry of aniracetam is not well understood, and it is not known which specific mGluRs aniracetam modulates. Group I mGluRs activation increases α-secretase activity [57]. Group III mGluRs activation facilitates non-amyloidogenic cleavage of AβPP, may increase BDNF levels, and helps remove extracellular Aβ via glial phagocytosis [58]. Activating group III mGluRs may also increase α-secretase and inhibit β-secretase expression [59]. Interestingly, downregulating Group 5 mGluRs may have neuroprotective effects and may be helpful in the treatment of AD [60].

Indeed, a 2020 article in the *Journal of Alzheimer's Disease* detailed the therapeutic potential of modulating mGluRs for the treatment and prevention of AD [53].

SIDE EFFECTS

Aniracetam is well-tolerated in most clinical trials and does not increase liver enzymes [1]. However, it is not without side effects. The most common adverse events reported with aniracetam use were unrest, anxiety, uneasiness, and insomnia. Other unwanted side effects include urinary urgency, headache, vertigo, mild stomach pain, nausea, diarrhea, and rash. In clinical trials these effects were considered mild and did not necessitate withdrawal from the study [1].

Aniracetam is well-tolerated in the majority of clinical trials. One study of 109 elderly subjects took aniracetam or placebo for six months. Researchers wrote, "Tolerability of aniracetam was excellent" [61]. Another study of 115 subjects took aniracetam or placebo for six months. Researchers reported excellent tolerability [62].

Despite the high tolerability in clinical trials, healthcare practitioners are reporting unpleasant side effects in patients taking aniracetam. If the side effects of aniracetam are significantly impairing the quality of life, especially if they are impairing sleep—which is essential to brain health and memory consolidation—it is important for the patient and practitioner to determine if the cognitive-enhancing and neuroprotective benefits of aniracetam are worth enduring the side effects.

DISCUSSION

Aniracetam is a known cognitive enhancer and positive modulator of AMPA receptors and mGluRs. Multiple studies indicate that aniracetam likely increases α-secretase activity by increasing BDNF expression and positively modulating mGluRs. No research could be found in human or animal studies investigating the impact of aniracetam on Aβ accumulation or production. To the author's knowledge, this paper is the first evidence-based model proposing that aniracetam lowers Aβ production and accumulation.

LIMITATIONS

There is much we do not know regarding AD neurobiochemistry. Researchers generally agree that cleaving AβPP with α-secretase will be neuroprotective by reducing Aβ. However, there remain multiple unknown aspects of AβPP, α-secretase, and Aβ biology. For example, which α-secretases effectively cleave AβPP to produce neuroprotective sAβPPα, and which ones do not? What are all of the downstream substrates of α-secretase, and what are the impacts of chronically elevating α-secretase? To what extent does modulating α-secretase affect levels of inflammation (e.g., TNF)? Clinical trials lasting six months report that aniracetam is well tolerated [61, 62], though this does not guarantee that there are no long-term negative impacts of chronically upregulating α-secretase.

Indeed, increasing α-secretase activity may be a double-edged sword. Cleaving AβPP with α- and γ-secretases does prevent the production of Aβ, and it also creates the peptides sAβPPα and P3. While sAβPPα has neuroprotective effects, P3 may be neurotoxic. P3 has demonstrated neurotoxic effects *in vitro*, specifically increasing neuronal apoptosis [63]. Recent research from 2020 found P3 to have amyloidogenic properties [64].

The biochemistry of aniracetam is not fully understood. Aniracetam modulates mGluRs, but does it modulate group I and/or group III mGluRs to the point of increasing α-secretase expression and increasing Aβ clearance? We do not know which α-secretase (e.g., ADAM9, ADAM10, ADAM19) aniracetam upregulates, nor which α-secretases cleave AβPP. Does aniracetam as a monotherapy, or used in tandem with other cholinergics or BDNF agonists, significantly reduce Aβ and slow down the progression of AD?

FUTURE RESEARCH

Because aniracetam has known cognitive and behavioral benefits in humans with mild cognitive impairment and early-stage AD [1, 61,65, 66], and aniracetam has a high level of tolerability and safety, human clinical trials could start immediately. I recommend starting with a 6-month crossover trial in adults with mild cognitive impairment. Ideally, researchers would measure cognition, serum BDNF levels, and Aβ using PET scans, at baseline and at every three months of the study. Subjects would be given 1,500 mg/day of aniracetam, taken with a source of fat to increase bioavailability (e.g., coconut oil, olive oil, or with food). To reduce potential side-effects, subjects could take a methylated B-complex vitamin and 1,200 mg of Alpha GPC with their aniracetam dose.

Further research is required to specify which mGluRs aniracetam modulates and which specific α-

secretase or secretases aniracetam activates. Future animal studies could also investigate the downstream impact of chronically increasing α-secretase activity. I recommend starting by investigating if a daily dose of aniracetam (50 mg/kg) in rats significantly increases BDNF expression and which specific mGluRs groups aniracetam modulates.

AUTHOR CONTRIBUTIONS

Robert William Love (Conceptualization; Writing – original draft; Writing – review & editing).

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CONFLICT OF INTEREST

The author has no conflict of interest to report.

DATA AVAILABILITY

All data are available in the main text.

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