Dementia and Depression: Biological Connections with Amyloid β Protein

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Abstract

Dementia is an umbrella term for a broad group of age-associated neurodegenerative diseases. It is estimated that dementia affects 50 million people worldwide and that Alzheimer's disease (AD) is responsible for up to 75% of cases. Small extracellular senile plaques composed of filamentous aggregates of amyloid β (Aβ) protein tend to bind to neuronal receptors, affecting cholinergic, serotonergic, dopaminergic, and noradrenergic neurotransmission, leading to neuroinflammation, among other pathophysiologic processes, and subsequent neuronal death, followed by dementia. The amyloid cascade hypothesis points to a pathological process in the cleavage of the amyloid precursor protein (APP), resulting in pathological Aβ. There is a close relationship between the pathologies that lead to dementia and depression. It is estimated that depression is prevalent in up to 90% of individuals diagnosed with Parkinson's disease, with varying severity, and in 20 to 30% of cases of Alzheimer's disease. The hypothalamic pituitary adrenal (HPA) axis is the great intermediary between the pathophysiological mechanisms in neurodegenerative diseases and depression. This review discusses the role of Aβ protein in the pathophysiological mechanisms of dementia and depression, considering the HPA axis, neuroinflammation, oxidative stress, signaling pathways, and neurotransmission.

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ABSTRACT

Dementia is an umbrella term for a broad group of age-associated neurodegenerative diseases. It is estimated that dementia affects 50 million people worldwide and that Alzheimer's disease (AD) is responsible for up to 75% of cases. Small extracellular senile plaques composed of filamentous aggregates of amyloid β (Aβ) protein tend to bind to neuronal receptors, affecting cholinergic, serotonergic, dopaminergic, and noradrenergic neurotransmission, leading to neuroinflammation, among other pathophysiologic processes, and subsequent neuronal death, followed by dementia. The amyloid cascade hypothesis points to a pathological process in the cleavage of the amyloid precursor protein (APP), resulting in pathological Aβ. There is a close relationship between the pathologies that lead to dementia and depression. It is estimated that depression is prevalent in up to 90% of individuals diagnosed with Parkinson's disease, with varying severity, and in 20 to 30% of cases of Alzheimer's disease. The hypothalamic pituitary adrenal (HPA) axis is the great intermediary between the pathophysiological mechanisms in neurodegenerative diseases and depression. This review discusses the role of Aβ protein in the pathophysiological mechanisms of dementia and depression, considering the HPA axis, neuroinflammation, oxidative stress, signaling pathways, and neurotransmission.

Keywords: Dementia, Depression, Amyloid β protein, Hypothalamic pituitary adrenal axis, Neurodegeneration.

Introduction

Dementia encompasses a wide range of neurodegenerative diseases linked to aging. It is a medical condition in which there is a deterioration in a person's cognitive abilities compared to a previous period over several months or years. It mainly affects memory but can also impair other functions such as language, attention, orientation, judgment, and planning. Age is directly related to the risk of developing dementia, with a rate of 5 to 10 cases per 1,000 person-years between the ages of 64 and 69. It can increase significantly to 40 to 60 cases per 1,000 person-years in the 80 to 84 age group.[1]

On a global scale, around 50 million people face the challenge of dementia today. Alzheimer's disease (AD) accounts for up to 75% of dementia cases[2]and is predicted to grow to 152 million by 2050. This increase will be particularly pronounced in countries with low- and middle-income families, home to approximately two-thirds of the population affected by dementia. Dementia affects the individuals directly involved, their families, and the global economy, generating costs estimated at around 1 trillion dollars annually.[3]

The relationship between depression and dementia is complex and not yet fully understood. There are divergent hypotheses about how these conditions are related and the neurobiological mechanisms involved. However, there is compelling evidence that depression early in life can increase the risk of dementia later in life and that late-life depression can be a precursor to dementia. Furthermore, both conditions present similarities in terms of neurobiological changes. It is suggested that white matter impairments may involve shared risk factors or typical patterns of neuronal damage between depression and dementia.[4]

Both depression and dementia, although considered distinct clinical entities, have some common characteristics. Among these similarities are attention and working memory impairments, sleep pattern disturbances, and social and occupational function impairments. Furthermore, there are potential changes in biological mechanisms that link depression to dementia. Among the biological changes are vascular diseases, dysfunctions in the hypothalamic-pituitary-adrenal (HPA) axis, dysregulating glucocorticoid hormones, hippocampal atrophy, accumulation of β-amyloid plaques, inflammatory changes and deficiencies in neural growth factors.[5]These connections may help clarify the complex relationship between these two clinical conditions.

Hippocampal atrophy and the presence of β-amyloid plaques in the central nervous system (CNS) are considered diagnostic indicators of AD. This condition is characterized by the accumulation of β-amyloid and

tubulin-associated unit (TAU) proteins, constituting the main components of neuritic plaques and neurofibrillary tangles (NFTs) in AD pathology.[6]Studies have shown that both β-amyloid protein plaques and TAU protein tangles accumulate in more significant quantities in the hippocampus of AD patients who also suffer from depression compared to those AD patients who have no history of depression.[7]Furthermore, β-amyloid appears to be considered the leading triggering agent of the sequence of events that culminates in the death of neurons and the development of AD. Therefore, a plausible mechanism connecting depression to AD involves the formation of β-amyloid plaques.[8]

Amyloid and TAU Proteins

The scientific literature identifies the amyloid protein as a biomarker for staging AD severity and helps investigate clinical prognosis. Other neurodegenerative pathologies also have amyloid protein as a causal background. Neurodegeneration after ischemic stroke has similarities with neurodegeneration in AD, as both pathologies have risk factors in common, such as age, hyperlipidemia, hypertension and diabetes, the presence of neuroinflammation, and the presence of amyloid protein.[9]

Amyloid protein is described as the main protein found in diseases related to aging, such as AD and Parkinson's disease (PD), dementia with Lewy bodies (DLB), Huntington's disease (HD), vascular dementia (VaD) and frontotemporal dementia (FTD). The "Amyloid Cascade Hypothesis" (figure 1) predicts the formation of extracellular senile plaques with NFTs, composed of filamentous aggregates of amyloid-β protein (Aβ) as a possible initial pathological event of dementia and consistent treatment route for the disease.[2]These small plaques tend to bind to neuronal receptors affecting cholinergic, serotonergic, dopaminergic, and noradrenergic neurotransmission, leading to neuroinflammation and subsequent neuronal death, followed by dementia.[10]

Aβ, composed of 39-42 amino acids, is expressed physiologically in the body and results from the digestion of amyloid precursor protein (APP), which performs physiological functions in neuroplasticity. The amyloid cascade hypothesis points to a pathological process in the cleavage of APP that results in pathological Aβ. APP is cleaved near the cell membrane by a protease called α-$\sigma\epsilon\varsigma\rho\epsilon\tau\alpha\sigma\epsilon$. This action releases a soluble extracellular fragment, sAPPα. Crossing the membrane, a second cut is made by a protein complex called γ-$\sigma\epsilon\varsigma\rho\epsilon\tau\alpha\sigma\epsilon$, releasing a second intracellular peptide known as amyloid intracellular domain (AICD), a residual fragment between α-secretase and γ-$\sigma\epsilon\varsigma\rho\epsilon\tau\alpha\sigma\epsilon$.[11]

The cutting carried out by α-secretase is physiological. Still, in pathological situations, APP cleavage occurs further away from the cell membrane by the β-$\sigma\epsilon\varsigma\rho\epsilon\tau\alpha\sigma\epsilon$ enzyme, followed by γ-$\sigma\epsilon\varsigma\rho\epsilon\tau\alpha\sigma\epsilon$ cleavage. The Aβ fragment can have 40 or 42 residues, Aβ1-40 and Aβ1-42. The amino acid that lies between β (pathological) and γ (physiological) cleavage is in the constitution of β-$\alpha\mu\psi\lambda o\iota\delta$peptides (Aβ), which aggregate to form oligomers (oAβ), distinct misfolded proteins that mediate synaptic dysregulation, hyperactivity of microglia and astrocyte reactivity.[11]

The gradual accumulation and aggregation of Aβ peptides will initiate a cascade that will lead to synaptic changes in microglial and astrocytic activation, culminating in the release of cytokines and, consequently, an inflammatory response, TAU modification and progressive neuronal losses associated with neurotransmitter deficiencies and cognitive impairments.[12]The cytoskeleton structurally organizes neurons, a component partially formed by microtubules. The TAU protein is present on the microtubules' surface and helps stabilize them. Composed of 3 or 4 semi-homologous repeats of 31 or 32 amino acids, TAU undergoes a hyperphosphorylation process and receives a phosphate group, leaving the microtubule and becoming insoluble. Phosphorylated TAU units form small polymers called helical filaments, resulting in NFTs in more significant quantities. Without the TAU protein to stabilize microtubules, their breakdown and subsequent cell death or apoptosis occur.[13]

Hypothalamus Pituitary Adrenal (HPA) Axis and Amyloid Protein

The activity of the HPA axis occurs primarily in response to stress through the secretion of corticotropin-releasing hormone (CRH) by neurons in the paraventricular nucleus in the hypothalamus, which stimulates

the anterior pituitary gland to produce adrenocorticotropic hormone (ACTH). ACTH activates receptors in the adrenal gland, stimulating the release of glucocorticoids (GC) into the circulation.[14]

GCs can cross the blood-brain barrier and bind to their respective receptors in the CNS, which are predominant in the prefrontal cortex (PFC), hippocampus, and amygdala and, through mechanisms that still require further elucidation, induce amyloid protein accumulation and cognitive impairment.[14]Cortisol has even been shown to have a significant relationship as a risk predictor for AD development, showing an average increase three years before the clinical manifestations of the disease.[15]

The greater availability of soluble Aβ proteins results in a stressful state, a more excellent production of CRH, and increased GC levels in response, positively feedbacking the HPA axis. It has been shown that the HPA axis is the great intermediary between pathological mechanisms of depression and neurodegenerative diseases, mainly due to the distribution and activation of low-affinity glucocorticoid (GR) and mineralocorticoid (MR) receptors, whose action and greater prevalence it is strongly associated with both cognitive and memory processes and psychiatric disorders such as depression, including in individuals who have suicidal ideation.[16]

A preclinical trial in rats used a selective GR blocker and found a reduction in neurotoxic effects in several molecular mechanisms inherent to the central regulation of the HPA axis, correlating with improved emotional and cognitive behaviors in AD. The authors suggest the presence of a vicious cycle based on the persistent activation of GR, deregulating the negative feedback pathways of the HPA axis, as well as culminating in structural changes in the PFC and hypothalamus, which are important regions for the accessory control of CRH production.[14]

A study showed that Aβ1-42 oligomers can impair learning and memory capacity in mice, associated with elevated levels of CRH, corticosterone, and greater expression of GR in the PFC and hippocampus. Due to this induced hyperactivity of the HPA axis, there is a negative regulation in the levels of cyclic adenosine monophosphate (cAMP), causing a lower phosphorylation of neuroprotective factors such as cAMP response element-binding protein (pCREB) and brain-derived neurotrophic factor (BDNF), which reinforces the cognitive impairment of AD.[17]

Another analysis carried out with cerebroventricular injection of Aβ25-35 oligomers observed an increase in depressive and anxiety symptoms in rats, as well as being associated with an increase in corticosterone induced by stress and hyperactivity of the HPA axis through GR in the hippocampal region.[18]Furthermore, a prospective cohort study showed that individuals with Aβ aggregates in imaging tests and high plasma cortisol levels have more pronounced and accelerated effects on scores of cognitive decline, episodic memory, and executive function.[19]

Neuroinflammation and Amyloid Protein

Neuroinflammation is inherent to the pathophysiology of depression and dementia. The literature has indicated that the inflammatory process in nervous tissue is mediated mainly by the gradual increase in β-amyloid load and the deregulated activity of microglia. The primary function of microglia is to promote neuroprotection, primarily through the phagocytosis of oAβ and, therefore, the loss of this capacity can accentuate the formation of amyloid aggregates which, when recognized by Toll-like receptors (TLR), induce inflammation, guided by the formation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes, with loss of synaptic communication and diffuse neuronal damage.[20]

The presence of NLRP3 inflammasome was associated with prolonged exposure to corticosterone and consequent greater activation of the HPA axis in mice with depressive behaviors.[21]Specific inhibition of NLRP3 reduced local neuronal injury and exerted control over Aβ accumulation and TAU protein hyperphosphorylation, alleviating depressive behavior and cognitive decline in rodents.[22]

Tumor necrosis factor alpha (TNF-α), in the context of neurodegenerative diseases, plays a role in mediating the processes of necroptosis, a pathway of cell death programmed by the activation of receptors interacting serine/threonine kinase 1 and 3 (RIPK1 and RIPK3) and mixed lineage kinase domain-like (MLKL). This

process is responsible for the massive release of other classes of cytokines, such as C-X-C motif chemokine ligands 8 and 1 (CXCL8 and CXCL1).[23]

The pronounced presence of pro-inflammatory proteins implies toxic effects on neural tissue, mainly due to the activation of the kynurenine (KP) pathway in specific regions important for cognitive and emotional control. Cytokines, especially interleukin-1 (IL-1) and interferon-gamma (IFN-γ), in addition to the presence of Aβ, stimulate the enzyme indoleamine-2,3-dioxygenase (IDO). The enzyme tryptophan-2,3-dioxygenase (TDO) functionality is positively influenced by corticosteroids, considering that corticosteroids such as cortisol act as signals to increase TDO activity. When TDO is more active, more tryptophan is converted into neurotoxic metabolites through the KP. This increase in TDO activity contributes to the deposition of harmful metabolites derived from tryptophan, affecting neural tissue and specific areas necessary for cognitive and emotional control.[24]

Oxidative Stress and Amyloid Protein

The etiological process of AD is associated with oxidative imbalance. The histopathological characteristic of the disease is related to NFTs and senile plaques composed of Aβ that have metallic aggregates such as copper, iron, or zinc ions. When these ions are part of the redox reaction, their aggregation into the amyloid protein can trigger the formation of reactive oxygen species (ROS). Increased oxidative stress and consequent changes in metabolism cause local damage through lipid deperoxidation, mitochondrial dysfunction, and damage to protein structure and function.[25]

Imaging methods showed increased oxidative damage due to Aβ deposition associated with lower glutathione and superoxide dismutase (SOD) activity in mice with AD.[26]Gene expression mapping in AD patients showed a profile highly associated with oxidative stress, with genes related to immune exhaustion, damage to transcription factors, and mutations in genes promoting protective responses.[27]

It has been reported that rats with depressive-like behaviors induced by Aβ have decreased levels of serotonin (5-HT) and norepinephrine (NA) and, in contrast, increased levels of tryptophan (TRP) and kynurenine (KYN) and high concentrations of ROS in the PFC, and consequent establishment of a neuroinflammatory state with local tissue damage (Figure 2). Pharmacotherapy aimed at inhibiting IDO has demonstrated efficacy in controlling depression, reversing 5-HT levels, and oxidative stress in animal models exposed to the accumulation of β-amyloid protein.[28]

Associated with the neuroinflammatory state and depressive behavior, producing metabolites by KP such as 3-hydroxy kynurenine (3-HK) and KYN interfere with cellular respiration, inhibiting mitochondrial complexes and, consequently, leading to energy losses. The inhibition of glutamine synthesis, resulting in glutamate accumulation, aggravates oxidative stress by hyperactivating NMDA and AMPA receptors, disrupting intracellular Ca^{2+} homeostasis. These glutamatergic events destabilize the cell membrane, causing cytotoxicity and inducing neuronal death.[29]

Excessive ROS production by dysregulated mitochondrial activity is directly associated with increased expression of AMPA and NMDA receptors and impaired glutamatergic signaling with Ca^{2+}overload and excitotoxicity in cell cultures with frontotemporal dementia (FTD) induced *invitro* .[30]A test in mice demonstrated that Aβ neurotoxicity is due to the high microglial sensitivity to the presence of this protein. Aβ1-42 oligomers led to increased mitochondrial ROS production, high extracellular glutamate levels, and neuronal death due to the rapid increase in calcium.[31]

Αμψλοιδ β Προτειν, Σιγναλινγ Πατηωαψς, ανδ Νευροτρανσμισσιον

Aβ accumulation interferes with complex intracellular signaling pathways, including those essential for the inflammatory response. Increased Aβ in the CNS can trigger a chronic inflammatory response, which is closely linked to the activation of glial cells and the production of pro-inflammatory cytokines.[32]

This disturbance in intracellular signaling pathways and interference with calcium homeostasis in nerve cells causes adverse effects on synaptic function. The accumulation of Aβ impairs communication between neurons

at synapses, resulting in dysfunctions in neurotransmission. Such synaptic changes are intrinsically related to the cognitive deficits characteristic of AD since effective communication between neurons is fundamental for adequate cognitive functioning.[33]

Aβ impairs synaptic plasticity, inhibiting long-term potentiation (LTP) and facilitating long-term depression (LTD). These synaptic changes caused impairments in object recognition memory. Furthermore, Aβ leads to the loss of dopaminergic terminals, reducing cortical dopamine levels. Administration of catecholamine reuptake blockers can reverse Aβ-induced synaptic dysfunction, restoring the ability to induce LTP after high-frequency stimulation (HFS) and improving memory.[34]

The complex relationship between APP, GABAergic neurotransmission, and synaptic plasticity was also investigated. The absence of APP in mouse models results in deficiencies in synaptic plasticity, including the formation of LTP, as well as behavioral and learning deficits. This is related to the reduction in GABA-mediated inhibitory postsynaptic current. APP also interacts with potassium-chloride cotransporter 2 (KCC2), affecting the levels of this protein and the intracellular concentration of chloride ions, which influences GABA-mediated inhibitory transmission. The absence of APP alters the post-translational regulation of KCC2, including its tyrosine phosphorylation and ubiquitination, resulting in changes in the inhibitory function of GABA.[35]

APP also interacts with the presynaptic $GABA_B$ receptor ($GABA_BR$), influencing the release of excitatory neurotransmitters and regulating synaptic plasticity. This interaction between APP and $GABA_BR$ plays an essential role in modulating neurotransmission. It may have implications for understanding the normal mechanisms of the nervous system and in pathological conditions, such as AD, in which APP plays a crucial role in beta-amyloid production. These findings highlight the complexity of interactions between neuronal components and open promising perspectives for developing therapeutic strategies targeting neurological disorders, such as AD, and for interfering with GABAergic transmission and synaptic plasticity.[35]

Another cellular signaling pathway that has been extensively studied as a possible mechanism involved in neurodegenerative and psychiatric diseases is the mammalian target of the rapamycin (mTOR) pathway. mTOR is a serine/threonine protein kinase complex that plays a crucial role in protein synthesis and degradation, cytoskeleton formation, and several diseases. Although the mechanism of mTOR is not entirely understood, there is evidence that points to the influence of subsets of NMDA receptors on GABAergic neurons, which reverse glutamate inhibition, stimulating mTOR and increasing synaptic signaling in several brain areas.[36]

An analysis of the expression levels of mTOR and its upstream and downstream components in hippocampal brain tissues obtained from control subjects and AD patients at different stages revealed a significant increase in the expression of RagC, an upstream component of mTOR, in AD patients in the initial, moderate and severe stages. Furthermore, in the severe stage of AD, there was a notable increase in the levels of mTORC1 and its downstream targets, S6 kinase 1, and regulatory associated protein of mTOR (Raptor).[37]These findings suggest that the impact of mTOR on the aging process may begin with forming of free radicals during aging, resulting in the presence of ROS that cause damage to DNA, proteins, lipids, and mitochondrial organelles. This culminates in a reduction in adenosine triphosphate (ATP) production, activating the ATP-sensitive AMP-activated protein kinase (AMPK) and inhibiting the mTOR pathway. These events culminate in the negative regulation of protein synthesis, as synthesis consumes ATP. Thus, there is a proportional increase in damaged proteins concerning healthy proteins.[38]

Furthermore, *post-mortem* studies have identified deficits in mTOR signaling in the limbic system structures of depressive individuals.[39]Drugs with NMDA receptor antagonist function stimulate mTOR and increase synapses.[22]A study involving liquiritigenin, a natural compound, in mice with chronic stress-induced depression showed that both liquiritigenin and the antidepressant fluoxetine improved depressive symptoms. Liquiritigenin restored neurotransmitter levels and activated the phosphatidylinositol-3-kinase (PI3K)/serine-threonine protein kinase family (AKT)/mTOR (PI3K/AKT/mTOR) cell signaling pathway, suggesting that liquiritigenin may have an effect antidepressant through this route. Therefore, the study

indicates that liquiritigenin may be helpful in treating chronic depression and suggests a potential role for the mTOR pathway in suppressing neurodegenerative diseases.[40]

These mechanisms play a fundamental role in dementia and thus represent essential components in elucidating the underlying mechanisms. Understanding these findings brings to light the intricate neuronal processes involved in neurodegeneration and opens promising perspectives for designing future therapeutic strategies and interventions targeting neurological disorders. This, in turn, instills hope in the continued search for effective treatments for AD and other related conditions.

Dementia, Depression and Amyloid Protein

A close relationship between depression and pathologies associated with dementia is widely documented. Depression is estimated to be prevalent in approximately 20 to 30% of individuals diagnosed with AD.[11]Depression and cognitive impairment related to dementia are common disorders in the elderly. The literature provides evidence that depression is a risk factor for the development of dementia and, in old age, is related to a prodrome of dementia.[4]A meta-analysis encompassing 32 studies with 62,598 participants and a follow-up period ranging from 2 to 17 years revealed that having experienced a depressive episode represents a significant risk factor for developing dementia.[41]

Studies focusing on late-life depression provide complementary evidence on the development of dementia. According to Saczynska et al.,[42]depression was associated with a significantly increased risk of incident dementia and AD in older men and women. Depression nearly doubled the risk of dementia and AD, even after controlling for factors such as age and sex. It is estimated that between 10% and 15% of AD cases are preceded by episodes of depression.[43]

Other research suggests that depression may be a psychological response to AD and the difficulties of coping with the diagnosis. Depression is also described as a consequence of AD, with a higher incidence in patients with early-onset AD than those with late-onset AD, possibly related to lifestyle changes. In later stages, the evolution of AD is accompanied by a reduction in depressive symptoms due to the reduction of emotions and their expression resulting from cognitive impairment.[44]

Several mechanisms have been associated with the relationship between depression and neuronal damage, including inflammatory processes, increased production of glucocorticoids, accumulation of β-amyloid protein, and formation of NFTs. These mechanisms can result in damage to brain regions such as the hippocampus. These connections between depression and neuronal damage not only directly contribute to the development of dementia but also decrease cognitive reserve, which can lead to the early and frequent emergence of cognitive impairment.[7]

In this context, the hypothesis that hyperperfusion and atrophy of brain areas, such as the anterior cingulate cortex, precuneus, and parietal lobule, as well as changes in receptors, such as N-methyl-D-aspartate (NMDAr), may be related to depressive symptoms and the progression of AD.[44]NMDAr is a receptor for the neurotransmitter glutamate that plays a fundamental role in synaptic plasticity, memory formation, and excitotoxicity, which has been associated with the pathophysiology of several diseases, including AD.[45]

Antidepressant medications may slow the progression of dementia in people with mild cognitive impairment (MCI) and depression. A 2017 study showed that long-term use of the antidepressant citalopram, a selective serotonin reuptake inhibitor (SSRI), for more than four years was associated with a delay of about three years in the progression of MCI to AD.[46]

Studies have found changes in glutamate levels in depression and AD, indicating a dysfunction in the NMDA receptor signaling pathway. The presence of Aβ in AD affects glutamatergic signaling via NMDAr, suggesting the possibility of developing NMDAr-modulating drugs with potential anti-dementia effects.[47]

Depression is frequently diagnosed in patients with cognitive and affective disorders, with cognitive impairments related to brain amyloid deposits and NFTs. In research involving young (2.5 months) and old (13 months) Brattleboro rats to evaluate the transcription of specific genes related to neurodegenerative diseases,

a link between dementia and neurodegeneration was found with the APP and the mitogen-activated protein kinase gene (MAPK1), associated with NFTs formed by the TAU protein, and the beta-actin gene that highlighted changes in increased cortical activity in elderly rats, indicating that age-dependent transcriptional changes can influence development of AD and other neurodegenerative disorders.[48]

In correlating depression as a significant risk factor for dementia, mainly due to the accumulation of Aβ peptide in the brain, a pivotal study involving elderly male mice carrying specific gene variants related to AD, Aβ load, and cognitive impairment yielded crucial insights. The study revealed a notable accumulation of Aβ in these mice, forming aggregated amyloid plaques. This accumulation not only indicated a direct link between depression and altered monoaminergic systems but also served as a vital indicator of changed functionality associated with the early stages of AD-related diseases.[49]

AD transgenic mice showed depressive and anxiety-like behaviors, parallel with increased Aβ deposition, TAU hyperphosphorylation, oxidative damage, inflammatory cytokines increase, and microgliosis in hippocampal and cortical tissue. A long-term exercise protocol significantly reduced anxious and depressive-like behaviors and brain biological damage.[50]

Final Considerations and Conclusions

Dementia is a degenerative disease characterized by the accumulation of Aβ proteins and is clinically manifested through global cognitive decline. These aggregates mediate the pathophysiology of several diseases where there is damage to nervous tissue through neuroinflammation and oxidative stress processes. In this article, we showed that Aβ accumulation causes failures in synapses and, consequently, in the activation of microglial cells, causing an uncoordinated inflammatory response with a large concentration of cytokines, inflammasomes, and cell migration. Furthermore, we point to dysfunctions of the HPA axis, in response to chronic systemic stress, as an intermediary in the biological processes of both diseases, especially in the neurotoxic effect induced by excess GC in essential areas of cognitive and emotional regulation, such as the PFC and hippocampus. Likewise, neuronal communication is impaired, emphasizing the decrease in synaptic plasticity mediated by GABAergic signaling and the mTOR pathway. Despite the findings described in the literature, the association between depression and dementia requires further elucidation, especially in aspects that delimit epigenetic regulation and intracellular response mechanisms to chronic stress induced by Aβ accumulation. Therefore, we suggest conducting new studies that seek to investigate this association and produce more assertive and specific potential therapeutic targets for these disorders.

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References

1. Burlá C, Camarano AA, Kanso S, Fernandes D, Nunes R. Panorama prospectivo das demências no Brasil: um enfoque demográfico. *Ciênc Saúde Coletiva*. 2013;18(10):2949-2956. doi:10.1590/S1413-81232013001000019

2. Sáiz-Vazquez O, Puente-Martínez A, Pacheco-Bonrostro J, Ubillos-Landa S. Blood pressure and Alzheimer's disease: A review of meta-analysis. *Front Neurol*. 2023;13:1065335. doi:10.3389/fneur.2022.1065335

3. Patterson C. World alzheimer report 2018. Published online 2018.

4. Bennett S, Thomas AJ. Depression and dementia: Cause, consequence or coincidence? *Maturitas*. 2014;79(2):184-190. doi:10.1016/j.maturitas.2014.05.009

5. Hakim A. Perspectives on the complex links between depression and dementia. *Front Aging Neurosci*. 2022;14:821866. doi:10.3389/fnagi.2022.821866

6. Morishima-Kawashima M, Ihara Y. Alzheimer's disease: ?-Amyloid protein and tau. *J Neurosci Res.* 2002;70(3):392-401. doi:10.1002/jnr.10355

7. Rapp MA, Schnaider-Beeri M, Purohit DP, Perl DP, Haroutunian V, Sano M. Increased Neurofibrillary Tangles in Patients With Alzheimer Disease With Comorbid Depression. *Am J Geriatr Psychiatry.* 2008;16(2):168-174. doi:10.1097/JGP.0b013e31816029ec

8. Leinonen V, Koivisto AM, Savolainen S, et al. Amyloid and tau proteins in cortical brain biopsy and Alzheimer's disease. *Ann Neurol.* 2010;68(4):446-453. doi:10.1002/ana.22100

9. Pluta R, Ułamek-Kozioł M, Kocki J, et al. Expression of the Tau Protein and Amyloid Protein Precursor Processing Genes in the CA3 Area of the Hippocampus in the Ischemic Model of Alzheimer's Disease in the Rat.*Mol Neurobiol.* 2020;57(2):1281-1290. doi:10.1007/s12035-019-01799-z

10. Metaxas A, Thygesen C, Briting SRR, Landau AM, Darvesh S, Finsen B. Increased Inflammation and Unchanged Density of Synaptic Vesicle Glycoprotein 2A (SV2A) in the Postmortem Frontal Cortex of Alzheimer's Disease Patients.*Front Cell Neurosci.* 2019;13:538. doi:10.3389/fncel.2019.00538

11. Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, et al. Depression as a Risk Factor for Alzheimer's Disease: A Systematic Review of Longitudinal Meta-Analyses.*J Clin Med.* 2021;10(9):1809. doi:10.3390/jcm10091809

12. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. *Nat Rev Mol Cell Biol.* 2007;8(2):101-112. doi:10.1038/nrm2101

13. Miller RL, Dhavale DD, O'Shea JY, et al. Quantifying regional α -synuclein, amyloid β, and tau accumulation in lewy body dementia. *Ann Clin Transl Neurol.* 2022;9(2):106-121. doi:10.1002/acn3.51482

14. Canet G, Pineau F, Zussy C, et al. Glucocorticoid receptors signaling impairment potentiates amyloid-β oligomers-induced pathology in an acute model of Alzheimer's disease. *FASEB J.* 2020;34(1):1150-1168. doi:10.1096/fj.201900723RRR

15. Ennis GE, An Y, Resnick SM, Ferrucci L, O'Brien RJ, Moffat SD. Long-term cortisol measures predict Alzheimer disease risk. *Neurology.* 2017;88(4):371-378. doi:10.1212/WNL.0000000000003537

16. Mifsud KR, Kennedy CLM, Salatino S, et al. Distinct regulation of hippocampal neuroplasticity and ciliary genes by corticosteroid receptors. *Nat Commun.* 2021;12(1):4737. doi:10.1038/s41467-021-24967-z

17. Lv J, Chen L, Zhu N, et al. Beta amyloid-induced time-dependent learning and memory impairment: involvement of HPA axis dysfunction. *Metab Brain Dis.* 2020;35(8):1385-1394. doi:10.1007/s11011-020-00613-3

18. Esmaeili MH, Bahari B, Salari AA. ATP-sensitive potassium-channel inhibitor glibenclamide attenuates HPA axis hyperactivity, depression- and anxiety-related symptoms in a rat model of Alzheimer's disease.*Brain Res Bull.* 2018;137:265-276. doi:10.1016/j.brainresbull.2018.01.001

19. Pietrzak RH, Laws SM, Lim YY, et al. Plasma Cortisol, Brain Amyloid-β, and Cognitive Decline in Preclinical Alzheimer's Disease: A 6-Year Prospective Cohort Study. *Biol Psychiatry Cogn Neurosci Neuroimaging.* 2017;2(1):45-52. doi:10.1016/j.bpsc.2016.08.006

20. Bisht K, Sharma K, Tremblay MÈ. Chronic stress as a risk factor for Alzheimer's disease: Roles of microglia-mediated synaptic remodeling, inflammation, and oxidative stress. *Neurobiol Stress.* 2018;9:9-21. doi:10.1016/j.ynstr.2018.05.003

21. Qin Z, Shi DD, Li W, et al. Berberine ameliorates depression-like behaviors in mice via inhibiting NLRP3 inflammasome-mediated neuroinflammation and preventing neuroplasticity disruption. *J Neuroinflammation.* 2023;20(1):54. doi:10.1186/s12974-023-02744-7

22. Li JM, Hu T, Zhou XN, et al. The involvement of NLRP3 inflammasome in CUMS-induced AD-like pathological changes and related cognitive decline in mice. *J Neuroinflammation*. 2023;20(1):112. doi:10.1186/s12974-023-02791-0

23. Zhu K, Liang W, Ma Z, et al. Necroptosis promotes cell-autonomous activation of proinflammatory cytokine gene expression. *Cell Death Dis*. 2018;9(5):500. doi:10.1038/s41419-018-0524-y

24. Sharma VK, Singh TG, Prabhakar NK, Mannan A. Kynurenine Metabolism and Alzheimer's Disease: The Potential Targets and Approaches. *Neurochem Res*. 2022;47(6):1459-1476. doi:10.1007/s11064-022-03546-8

25. Rummel NG, Butterfield DA. Altered Metabolism in Alzheimer Disease Brain: Role of Oxidative Stress. *Antioxid Redox Signal*. 2022;36(16-18):1289-1305. doi:10.1089/ars.2021.0177

26. Emoto MC, Sato-Akaba H, Hamaue N, et al. Early detection of redox imbalance in the APPswe/PS1dE9 mouse model of Alzheimer's disease by in vivo electron paramagnetic resonance imaging. *Free Radic Biol Med*. 2021;172:9-18. doi:10.1016/j.freeradbiomed.2021.05.035

27. Zhang Y, Kiryu H. Identification of oxidative stress-related genes differentially expressed in Alzheimer's disease and construction of a hub gene-based diagnostic model. *Sci Rep*. 2023;13(1):6817. doi:10.1038/s41598-023-34021-1

28. Tucci P, Bove M, Sikora V, et al. Glucoraphanin Triggers Rapid Antidepressant Responses in a Rat Model of Beta Amyloid-Induced Depressive-like Behaviour.*Pharmaceuticals*. 2022;15(9):1054. doi:10.3390/ph15091054

29. Sharma VK, Singh TG, Mehta V. Stressed mitochondria: A target to intrude alzheimer's disease. *Mitochondrion*. 2021;59:48-57. doi:10.1016/j.mito.2021.04.004

30. Esteras N, Kopach O, Maiolino M, et al. Mitochondrial ROS control neuronal excitability and cell fate in frontotemporal dementia. *Alzheimers Dement*. 2022;18(2):318-338. doi:10.1002/alz.12394

31. Jekabsone A, Jankeviciute S, Pampuscenko K, Borutaite V, Morkuniene R. The Role of Intracellular Ca2+ and Mitochondrial ROS in Small Aβ1-42 Oligomer-Induced Microglial Death. *Int J Mol Sci*. 2023;24(15):12315. doi:10.3390/ijms241512315

32. Blennow K, Zetterberg H. The Past and the Future of Alzheimer's Disease Fluid Biomarkers. Perry G, Avila J, Tabaton M, Zhu X, eds. *J Alzheimers Dis*. 2018;62(3):1125-1140. doi:10.3233/JAD-170773

33. Shankar GM, Li S, Mehta TH, et al. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med*. 2008;14(8):837-842. doi:10.1038/nm1782

34. Moreno-Castilla P, Rodriguez-Duran LF, Guzman-Ramos K, Barcenas-Femat A, Escobar ML, Bermudez-Rattoni F. Dopaminergic neurotransmission dysfunction induced by amyloid-β transforms cortical long-term potentiation into long-term depression and produces memory impairment. *Neurobiol Aging*. 2016;41:187-199. doi:10.1016/j.neurobiolaging.2016.02.021

35. Tang X, Drotar J, Li K, et al. Pharmacological enhancement of *KCC2* gene expression exerts therapeutic effects on human Rett syndrome neurons and*Mecp2* mutant mice. *Sci Transl Med*. 2019;11(503):eaau0164. doi:10.1126/scitranslmed.aau0164

36. Abelaira HM, Réus GZ, Neotti MV, Quevedo J. The role of mTOR in depression and antidepressant responses. *Life Sci*. 2014;101(1-2):10-14. doi:10.1016/j.lfs.2014.02.014

37. Sun YX, Ji X, Mao X, et al. Differential Activation of mTOR Complex 1 Signaling in Human Brain with Mild to Severe Alzheimer's Disease. *J Alzheimers Dis*. 2013;38(2):437-444. doi:10.3233/JAD-131124

38. Yang G, Humphrey SJ, Murashige DS, et al. RagC phosphorylation autoregulates mTOR complex 1. *EMBO J*. 2019;38(3):e99548. doi:10.15252/embj.201899548

39. Chandran A, Iyo AH, Jernigan CS, Legutko B, Austin MC, Karolewicz B. Reduced phosphorylation of the mTOR signaling pathway components in the amygdala of rats exposed to chronic stress. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;40:240-245. doi:10.1016/j.pnpbp.2012.08.001

40. Tao W, Dong Y, Su Q, et al. Liquiritigenin reverses depression-like behavior in unpredictable chronic mild stress-induced mice by regulating PI3K/Akt/mTOR mediated BDNF/TrkB pathway. *Behav Brain Res*. 2016;308:177-186. doi:10.1016/j.bbr.2016.04.039

41. Prince M, Albanese E, Guerchet M, Prina M. *World Alzheimer Report 2014. Dementia and Risk Reduction: An Analysis of Protective and Modifiable Risk Factors.*Alzheimer's Disease International; 2014.

42. Saczynski JS, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Depressive symptoms and risk of dementia: the Framingham Heart Study. *Neurology*. 2010;75(1):35-41. doi:10.1212/WNL.0b013e3181e62138

43. Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr Opin Psychiatry*. 2011;24(6):461-472. doi:10.1097/YCO.0b013e32834bb9d4

44. Botto R, Callai N, Cermelli A, Causarano L, Rainero I. Anxiety and depression in Alzheimer's disease: a systematic review of pathogenetic mechanisms and relation to cognitive decline. *Neurol Sci*. 2022;43(7):4107-4124. doi:10.1007/s10072-022-06068-x

45. Snyder EM, Nong Y, Almeida CG, et al. Regulation of NMDA receptor trafficking by amyloid-beta. *Nat Neurosci*. 2005;8(8):1051-1058. doi:10.1038/nn1503

46. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A, for the Alzheimer's Disease Neuroimaging Initiative. Impact of SSRI Therapy on Risk of Conversion From Mild Cognitive Impairment to Alzheimer's Dementia in Individuals With Previous Depression. *Am J Psychiatry*. 2018;175(3):232-241. doi:10.1176/appi.ajp.2017.17040404

47. Bukke VN, Archana M, Villani R, et al. The Dual Role of Glutamatergic Neurotransmission in Alzheimer's Disease: From Pathophysiology to Pharmacotherapy. *Int J Mol Sci*. 2020;21(20):7452. doi:10.3390/ijms21207452

48. Kálmán S, Pákáski M, Szucs S, et al. [The transcription of the amyloid precursor protein and tryptophan 2,3-dioxygenase genes are increased by aging in the rat brain]. *Ideggyogyaszati Szle*. 2009;62(9-10):326-332.

49. Nyarko JNK, Quartey MO, Baker GB, Mousseau DD. Can Animal Models Inform on the Relationship between Depression and Alzheimer Disease? *Can J Psychiatry Rev Can Psychiatr*. 2019;64(1):18-29. doi:10.1177/0706743718772514

50. Wu C, Yang L, Li Y, et al. Effects of Exercise Training on Anxious-Depressive-like Behavior in Alzheimer Rat. *Med Sci Sports Exerc*. 2020;52(7):1456-1469. doi:10.1249/MSS.0000000000002294