Open Access Research Journal of
Multidisciplinary Studies
Journals home page: https://oarjpublication/journals/oarjms/
ISSN: 2783-0268 (Online)

(REVIEW ARTICLE)

Biochemical mechanisms of Alzheimer's disease: Narrative Review

Iman Noori Mahmood Mahdi [1,*], Fatimah Yanadi Mohammed Ismail [2] and Nermen R. Ahmad [1]

[1] *Department of Chemistry, College of Science, University of Kirkuk, Kirkuk, Iraq.*
[2] *Department of Chemistry, College of Education for Women, University of Kirkuk, Kirkuk, Iraq.*

Open Access Research Journal of Multidisciplinary Studies, 2026, 11(02), 048-062

Publication history: Received on 26 February 2026; revised on 04 April 2026; accepted on 07 April 2026

Article DOI: https://doi.org/10.53022/oarjms.2026.11.2.0033

Abstract

The most debilitating form of neurodegeneration in the human brain is the alzheimer disease (AD) which incurs 60-70 percent of all the diagnosed cases of dementia globally. Current biochemistry has shown that this illness is not an acute phenomenon but a silent build up of molecular imbalances that start 20 or more years prior to the emergence of symptoms. Fundamentally, Alzheimer disease is a complex tragedy of the biochemical nature when three factors come together: first, the malfunction of the processing of the amyloid precursor protein (APP), leading to the appearance of toxic A B1 42 in the cerebral spinal fluid in concentration higher than 500 nmol/L, an A B1 42/ A B 0 ratio greater than the Secondly, over-phosphorylation of tau protein on particular loci including Thr181, Thr217 and Ser202/Thr205 (epitope AT8) is indicated by high plasma p-tau 181 levels of over 2.2 pg/mL and p-tau 217 levels of over 0.37 pg/mL. Thirdly, chronic oxidative stress is indicated by elevated urinary 8-OHdG levels above 12 nmol/mmol creatinine and serum malondialdehyde levels above 4.2 nmol/mL. This article explores these interconnected biochemical mechanisms and their measurable biomarkers to provide a comprehensive picture linking molecular interactions to detectable and diagnostic biological changes.

Keywords: Alzheimer's disease; Biochemical biomarkers; Aβ42; p-tau217; Oxidative stress; 8-OHdG; Neuroinflammation; IL-1β; APOE4; GSK-3β; NfL; GFAP

1. Introduction

Researchers have long been puzzled by a peculiar gap in Alzheimer's disease: brains that appear functionally normal but harbor a silent biochemical storm that will ravage them over decades [1]. This gap between biochemical and clinical timeline is perhaps the most profound complexity of the disease, and its greatest challenge to diagnosis and treatment [2]. Since Alois Alzheimer described the plaques and tangles in the brain of his patient Auguste Dieter in 1906, more than a century passed before researchers realized that these tissue changes were merely the culmination of a long and complex biochemical process spanning decades [3,4].

The aging population is fueling an unprecedented surge in the number of people affected: from 55 million currently to a projected 139 million by 2050, according to the 2023 Alzheimer's Disease International report [5]. Economic costs of this disease in the global arena are estimated at between 1.3 to 1.5 trillion a year, a figure that is bound to increase by two folds unless a disease-modifying treatment is found [6]. This dark fact has taken a great toll on science: almost 99 percent of clinical trials in the last 20 years have failed to yield any meaningful positive outcome and even the two recently approved drugs leucaena and donanemab are not a cure but only moderately beneficial [6].

The similarity between all these failures is that there is inadequate biochemical knowledge about the disease at its initial stages [7]. Clinical trials have mostly been carried out at the full symptomatic stage, when the brain has already lost 30 to 40 percent of its neurons in memory areas, and when A -depositional levels have elevated to levels that are not readily reversible [8]. It is here that the vital role of knowing about biochemical biomarkers comes in: it is the sole chance of

* Corresponding author: Iman Noori Mahmood Mahdi

realizing the disease prior to its complete destruction and also to measure the therapeutic actions in an accurate, objective way [9].

Pathochemistry of Alzheimer disease is multi-layered: molecular level is disrupted with secretase enzymes and accumulation of toxic peptides [10]. At cellular level mitochondria is damaged, microtubules are broken and cellular stress reactions are worsened. The neuroinflammation burst and microglia functions are enhanced at the tissue level [11]. On a systemic level, dozens of biomarkers, the chemical prints of this progressive damage, are increased in the cerebral fluid, blood and urine [12]. In order to see this complex biochemical network in as specific form as possible, this review looks at each disease mechanism within the context of its measurable biochemical signature, in an attempt to connect the molecular interactions to observable changes and, subsequently, to clinical relevance [13]. This review will cover the most important aspects of biochemical pathophysiology: APP metabolism and A2 formation and its markers in the cerebrospinal fluid and blood, tau phosphorylation and measurable p-tau forms, oxidative stress and its molecular products, neuroinflammation and its cytokines, mineral homeostasis, disruption of cellular signaling pathways and their enzymatic implications In each of the areas, the article is dedicated to the quantitative values and reference ranges distinguishing between the pathological and normal conditions, pointing to the interrelation between biochemistry and its diagnostic and therapeutic uses.

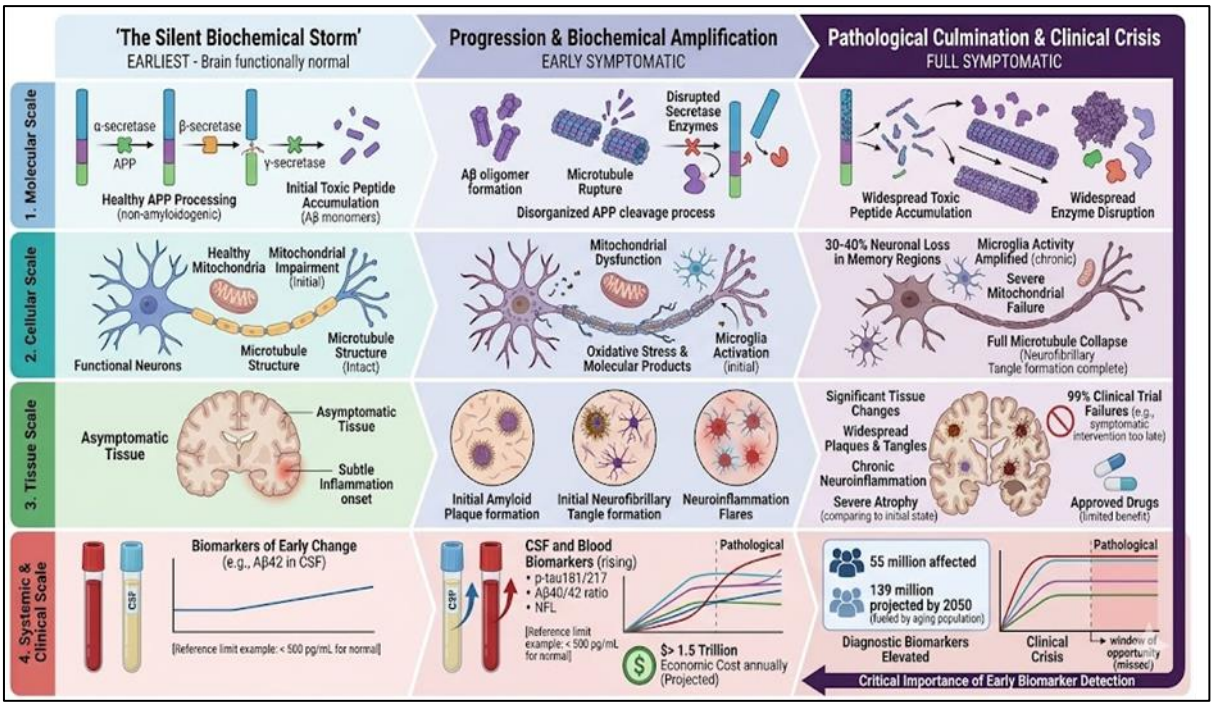

Figure 1 The Biochemical Timeline of Alzheimer's Disease Pathophysiology: From Silent Storm to Clinical Diagnosis.

2. Amyloid metabolism: Biochemistry from enzyme to plaque

2.1. APP protein and the balance between the two secretase pathways

The first biochemical substrate in the pathway of events in Alzheimer disease is Amyloid precursor protein (APP). APP is composed of 695 to 770 amino acids, and is a type I transmembrane protein, with an extension of the extracellular space across the plasma membrane to form a short cytoplasmic tail into the cell, depending on its projective isoform. This tail connects to adaptor proteins including Fe65 and XL that control the intracellular kinetics of APP, and route it to different metabolic directions [14].

A delicate enzymatic race biochemically determines the fate of APP: in the non-amyloid pathway, APP is cleaved into the sAPPalpha fragment (mass 100120 kDa) by alpha-secretases (ADAM10 and ADAM17 are its most prominent representatives) between the amino acids Lys16 and Leu17 of the A2 domain, which has neuroprote Conversely, BACE1 pathway activation is the initial step in amyloidogenesis: BACE1, an aspartyl protease that acts in an acidic environment (pH 4.5) in endosomes and the endoplasmic reticulum, cleaves APP at Asp1 of the A2 sequence to form the sAPP2 fragment and the C99 fragment, which remain in the membrane [1].

The 79 C99 fragment is then cleaved in the membrane by the 7-subunit protein complex, the 7-subunit -secretase complex which consists of presenilin (PSEN1 or PSEN2) as a catalytic subunit carrying catalytic diaspartyl, nicastrin as a substrate acceptor, and aph-1 and Pen-2 as regulatory subunits. This complex cleaves C99 at multiple sites within the membrane domain (ε, ζ, γ) via a sequential cleavage process that produces peptides ranging from 37 to 49 amino acids in length, the most prominent of which are Aβ40 (60–70% of production), Aβ42 (10–15%), and Aβ43 (rare but highly toxic) [17;18].

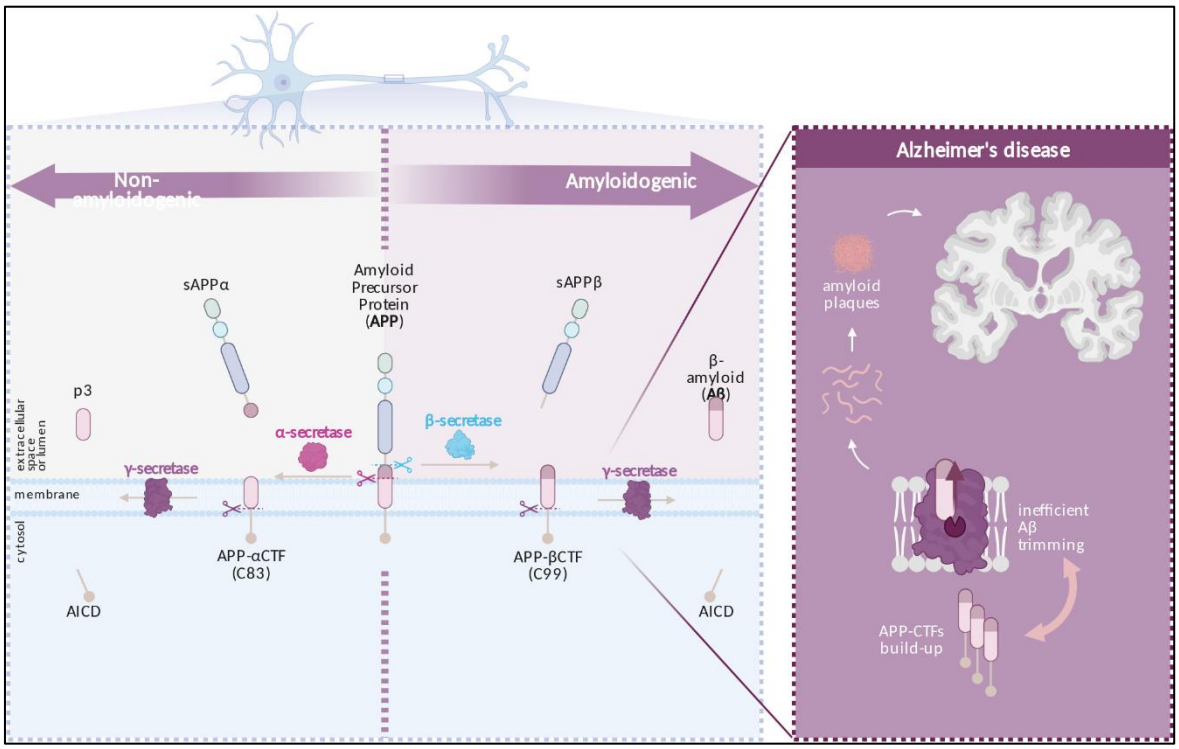

Figure 2 Proteolytic processing of the amyloid precursor protein (APP). The type I transmembrane protein APP undergoes initial cleavage by either α-secretase or β-secretase, entering the non-amyloidogenic (left) or amyloidogenic (right) pathway, respectively. In both pathways, a second proteolytic cleavage by γ-secretase releases the APP intracellular domain (AICD) into the cytosol. Cleavage of α-secretase-generated C-terminal fragments of APP (APP-αCTFs) by γ-secretase produces small p3 peptides, whereas cleavage of APP-βCTFs generates β-amyloid (Aβ) peptides of varying lengths. In Alzheimer's disease (right panel), decreased efficiency of γ-secretase processing may co-occur, leading to both the accumulation of APP-CTFs and the production of longer aggregation prone Aβ in the brain, ultimately forming amyloid plaques and driving widespread neurodegeneration. Figure created in BioRender

2.1.1. Biochemical indicator: Aβ42/Aβ40 ratio in cerebrospinal fluid

The A242/A20 ratio of A242 to A20 in cerebral spinal fluid (CSF) has become important biochemically as a measure of the dysfunction of GABA-secretase pathway and A242 deposition. In patients with Alzheimer, this ratio is decreased to less than 0.09 -0.10 (compared to 0.12 -0.15 in normal subjects), due to decreased CSF A42 concentration of the brain deposits to less than 500 pg/mL - the opposite effect of the high concentration of A42 in the CSF, indicating severe retention of A42 in brain It has been revealed that this low ratio is a preclinical biomarker since it is the first biomarker that is detectable before the onset of the symptoms by 15-25 years [19; 20].

2.2. Physical Chemistry of the Aβ42 Cluster

The unusual aggregating propensity of A2 is explained by its unique physicochemical characteristics: the two other amino acids, Ile41 and Ala42, contribute hydrophobicity to the carboxyl end of A 2, whereas the KLVFF (16-20) and GAIIGL (33-37) regions serve as nucleation seeds. Melting point (Tm) of A242 fibrous structures increases to approximately 80 C whereas it is approximately 60 C in A240, indicating that A242 aggregates are more thermostable and thus harder to dissociate. On the chemical level, the assembly process takes place in two stages: the primary nucleation stage, where the nucleus is formed from 6-12 monomers at a critical micelle concentration (CMC) of about 0.1-0.5 micromoles/L for Aβ42, and then the rapid elongation stage, where new units are rapidly added to form fibers [21].

Oligomers with masses ranging from 15 to 70 kilodaltons are the most biochemically toxic: they disrupt cell membrane channels by forming 1-2 nm diameter amyloid pores that allow an unregulated flow of calcium Ca^{2+} into the cell, raising the intracellular calcium concentration from the normal 100 nmol/L to 500-1000 nmol/L, which triggers signaling cascades, including the activation of calcineurin and CaMKII (calmodulin-dependent protein kinase II), which phosphorylate synaptic regulatory proteins and destroy synaptic plasticity [22;23].

2.3. Biochemical removal mechanisms and their limitations

The biochemical health of the human brain depends on three main Aβ clearance systems: the first is enzymatic and involves neprilysin (NEP), a metalloendopeptidase with a mass of 90–110 kDa that cleaves Aβ at multiple sites, and insulin degrading enzyme (IDE), which shares chemical pathways with insulin to bind to Aβ. NEP and IDE activity is reduced by 25–40% in the brains of Alzheimer's patients compared to healthy individuals of the same age [24]. The second is immunological, mediated by the LRP1 (Low-density Lipoprotein Receptor-related Protein 1) receptor on the blood-brain barrier, which binds Aβ-APOE and releases it into the peripheral circulation. A 30–50% reduction in LRP1 density has been observed in the brains of patients. The third is hydrodynamic and includes the glymphatic system, which works during deep sleep to remove protein waste, and its activity declines by up to 40 percent with aging, especially in chronic sleep disorders [25].

3. Tao Biochemistry: From Phosphorylation to Fibrils

3.1. Natural Tau: A protein without a fixed structure

Tau protein (TauMAPT) is a type of biochemically intrinsically disordered protein (IDP), or in other words it does not have a fixed three-dimensional structure at physiological temperatures. This gives it a tremendous structural flexibility, allowing it to react with microtubules with a high level of efficiency. There are 85 possible phosphorylation sites on Tau (80 Ser/Thr, 5 Tyr), with its longest projection (2N4R) estimated at about 79 kDa. Pathological phosphorylation however elevates its electrophoretic mobility and it appears as a 60-70 kDa protein on the SDS-PAGE [26].

In physiological conditions, tau is glycosylphosphorylated at about 2-3 positions and interacts with the microtubules through its four domains (or three in Figure 3R) to microtubule-binding repeats (MTBRs). This binding stabilizes the microtubule structures and makes transport of the vesicles at a rate of 200-400 mm/day in the authoritative direction and 20- 200 mm/day in the restorative direction possible [27].

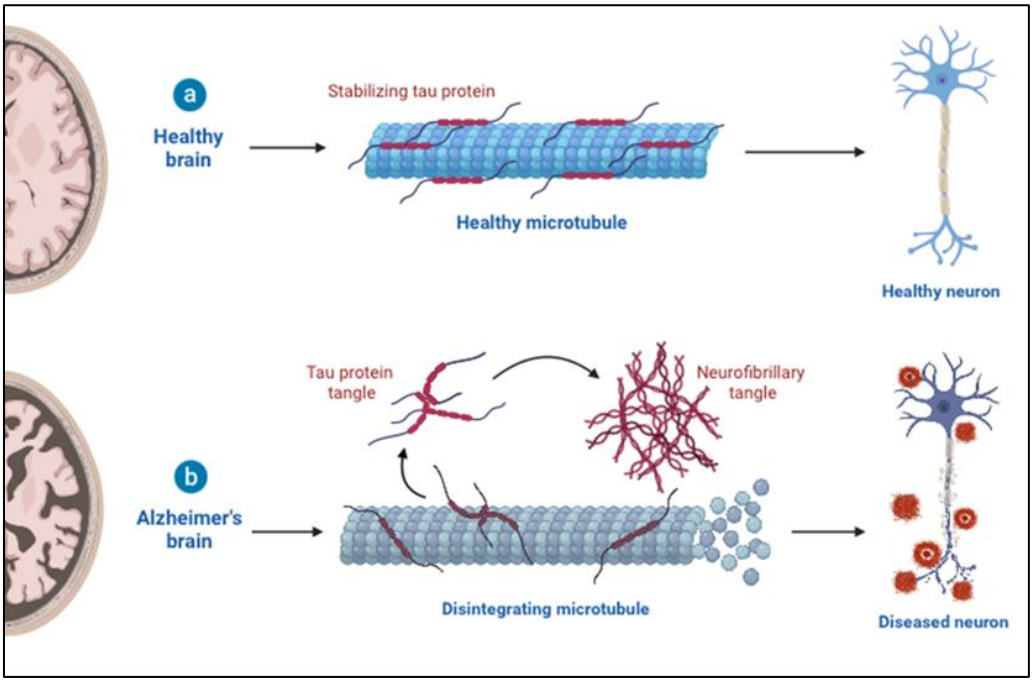

Figure 3 Pathogenesis of Tau Protein in Alzheimer disease

This diagram uses a comparison between a Healthy Brain (a) and an Alzheimer Disease Brain (b) in terms of cellular and molecular environment in which the neuronal integrity is disrupted. This figure is created in BioRender.

3.2. The chemical landscape of pathological phosphorylation

Tau pathological history starts when normal equilibrium is overridden by phosphorylation kinases. GSK-3B (Glycogen Synthase Kinase-3 Beta) is the highest in the pyramid of tau phosphorylation: this kinase phosphorylates over 42 tau loci, including Ser396, Ser404, Thr231 and Ser202/ Thr205 (the AT8 epitope complex). GSK-32 works best when CDK5 (Cyclin-Dependent Kinase 5) phosphorylates some of these sites prior to GSK-32 action as CDK5-p25 phosphorylates Thr231 and Ser235, thereby presenting a better substrate to GSK-32. Pathological studies show that the activity of GSK-3 in patient tissues is 2-4 times more active than in normal people, and the speed of p35-p25 cleavage is higher because of Calpain activation by the elevation of intracellular calcium [28].

3.2.1. Biochemical indicators of tau phosphorylation

The biochemical diagnosis of Alzheimer disease is based on the level of phosphorylated tau in cerebrospinal fluid (CSF) and plasma. In CSF, p-tau181 (phosphorylated tau at Thr181) is higher than under 6180 pg/mL in patients with Alzheimer, and less than 52 pg/mL in normal individuals, with minimal interlaboratory variation. A p-tau181 level exceeding 2.2 pg/mL is considered as a high chance of amyloid positivity with sensitivity of 85 percent and specificity of 90 percent in large studies [29; 30].However, p-tau217 (phosphorylated tau at Thr217) exhibits a more selective biochemical response to Alzheimer's disease: its plasma concentrations vary 5–7-fold in patients compared to healthy individuals (compared to twice that of p-tau181), making it the most accurate marker for differentiation. A 2020 TRIAD study revealed that p-tau217 in plasma can distinguish between Alzheimer's and frontotemporal dementia with an area under the curve (AUC) as high as 0.96 [31].

Elevated total-tau (t-tau) levels in cerebrospinal fluid serve as an indicator of the severity of axonal degeneration, exceeding 300-400 pg/ml in intermediate and advanced stages (compared to 200-250 in healthy individuals). However, what distinguishes t-tau biochemically is that it is elevated in many degenerative conditions (severe epilepsy, traumatic brain injury) and not exclusively in Alzheimer's disease, making it an indicator of injury rather than a disease indicator in the strict sense [32].

3.3. Paired twisted fibers and cytoskeletal collapse

When phosphorylated tau exceeds a critical concentration within the neuron, it initiates self-association via hydrophobic interactions and hydrogen bridges between MTBR domains. Primary oligomers form nuclear platforms to which additional tau is added to form double-helix twisted fibers (PHFs) with a double helix structure, nucleus-length 10 nm and a complete rotation every 80 nm. These fibers are deposited within the neuron to form synapses (NFTs) that exhibit characteristic fluorescence when stained with thioflavin-T and Congo Red dyes. The dangerous biochemical reversal of this accumulation is that the tubules become unstable, the axonal transport network collapses, and the dendritic and axonal terminals are deprived of vital logistical supplies of proteins and organelles, in a cycle of progressive atrophy culminating in cell death [33; 34].

4. Biochemistry of the cholinergic system

4.1. Acetylcholine Synthesis and Degradation Enzymes

Acetylcholine (ACH) is the axonal neurotransmitter in the circuits of attention, learning, and working memory. The biochemistry of this neurotransmitter is precisely determined by two enzymes: the first is choline acetyltransferase (ChAT), which synthesizes ACh from acetyl-CoA and choline according to the reaction: acetyl-CoA + choline → acetylcholine + CoA. This enzyme includes a bi-bi binding site that requires approximately 0.2 mmol/L of acetyl-CoA within the presynaptic terminals. A 50–90% reduction in ChAT activity in the prefrontal cortex, hippocampus, and basal forebrain has been documented in the middle–advanced stages of Alzheimer's disease [35; 36]. The second is acetylcholinesterase (ACHE), which hydrolyzes ACh in the synaptic cleft at a turnover rate of 25,000 acetylcholine molecules/second/enzyme molecule, making it one of the fastest known enzymes. In Alzheimer's disease, total AChE decreases due to neuronal loss, but the G1-associated AChE profile is relatively elevated and is used as a histological marker of amyloid activation [37].

4.2. ACh receptors and their biochemical significance

Nicotinic receptors (nAChRs) contain multiple subunits, the most prominent in the context of Alzheimer's disease being α4β2 and α7. α7 is characterized by its homopentameric structure and high calcium permeability (Ca^{2+} permeability ~5 times that of AMPA). Reduced α7 density in the hippocampus and prefrontal cortex of Alzheimer's patients, ranging from 35% to 60%, has been documented using radioligand binding techniques with α-Bungarotoxin. Most importantly, biochemically, Aβ42 peptides bind to α7 nAChR with high affinity (Kd ~ 5-10 nmol/L), a binding that alters receptor conduction and transforms it from a mediator of protective signaling to a facilitator of Aβ entry into the neuron, adding a new dimension to the dialectical relationship between amyloid and the cholinergic system [38; 39].

5. Oxidative stress: Free radical chemistry and molecular damage

5.1. Sources of ROS and the Hierarchy of Oxidative Damage

Oxidative stress in Alzheimer's disease depicts a radical imbalance between reactive oxygen species (ROS) and the antioxidant defense system. The main ROS originate from four parallel sources in diseased neurons: first, the mitochondrial electron transport chain, where approximately 2% of oxygen electrons leak to produce $O_2\bullet^-$ (superoxide); second, the Fenton reaction mediated by transition metals: $Fe_2^+ + H_2O_2 \rightarrow Fe_3^+ + HO\bullet + OH^-$, and $Cu^+ + H_2O_2 \rightarrow Cu_2^+ + HO\bullet + OH^-$; both reactions produce highly reactive hydroxyl radicals (HO•) (rate constant $k \sim 10^9$–10^{10} $M^{-1}s^{-1}$). Third, microglia NADPH oxidase (NOX2), which produces $O_2\bullet^-$ as part of the immune response. Fourth, nitric oxide oxidase (nNOS/iNOS), which produces NO• that reacts rapidly with $O_2\bullet^-$ to generate peroxynitrite ($ONOO^-$), capable of nitrating tyrosine residues in proteins (protein nitration) and disabling their functions [40; 41].

5.1.1. Biochemical indicators of oxidative stress

Molecular oxidation products provide a precise biochemical map of the extent of damage in Alzheimer's disease. Regarding lipid oxidation: 4-hydroxy-2-nonenal (4-HNE) increases in postmortem brain tissue from an average of 1–2 nmol/g in healthy individuals to 4–7 nmol/g in those with the disease. 4-HNE induces covalent modifications to cysteine (Cys), histidine (His), and lysine (Lys) residues in proteins, impairing their function. Serum malondialdehyde (MDA) rises between about 2-3 nmol/mL to 4-6 nmol/m. In relation to DNA oxidation: the most precise measure is 8-hydroxy-2'-deoxyguanosine (8-OHdG), the urinary levels of which rise in healthy people to about 6-8 nmol/mmol creatinine but in patients with Alzheimer, the level rises to 12-18 nmol/mmol. Concerning protein oxidation: Protein carbonyls rise in 1-2 nanomoles/mg of protein in healthy people to 3-5 nanomoles/mg in the affected people [42; 43].

5.2. Mitochondrial dysfunction and its biochemical effects

The oxidative stress of the Alzheimer disease is primarily located in mitochondria. Respiratory complex activity measurements show a progressive loss: the activity of complex I (NADH ubiquinone oxidoreductase) decreases by 25-35% and the activity of complex IV (Cytochrome c oxidoreductase) decreases by 20-50% in the temporal cortex and hippocampus. This impairment causes three consecutive biochemical effects: a drop in ATP production to less than 70 percent of normal energy, which causes a synaptic energy deficit; an increase in electron leakage and O 2 - generation; a drop in mitochondrial membrane potential (-180 mV) of -120 -140 mV, which signifies dying and inefficient mitochondria [44;45;46].

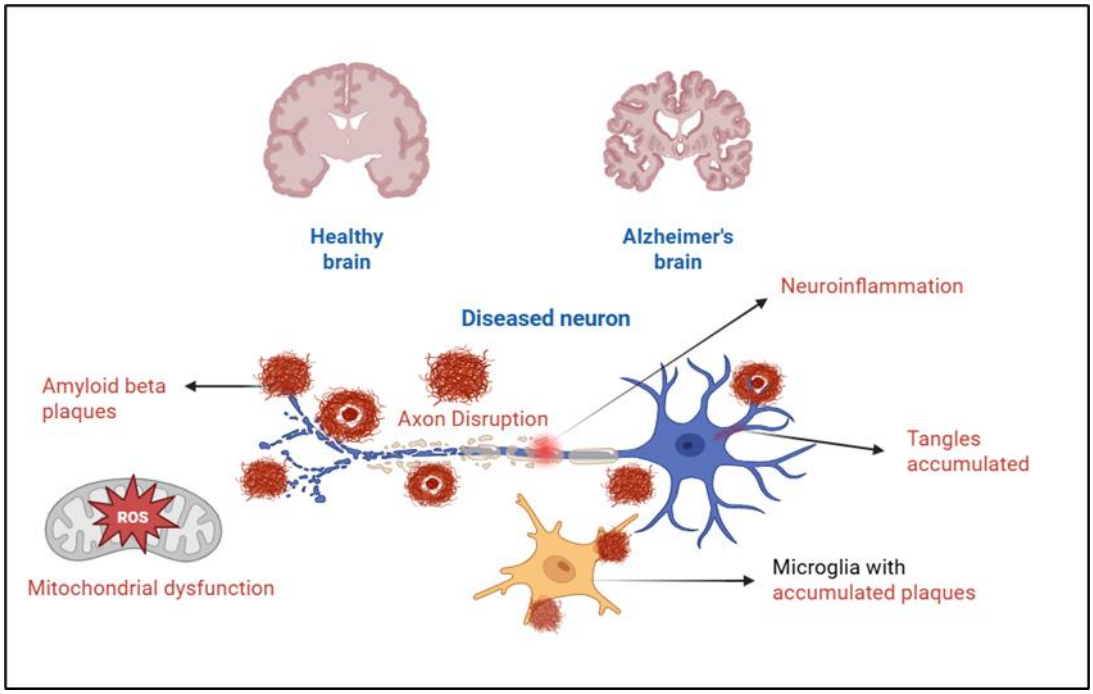

Figure 4 The image displays an Alzheimer's patient's brain with enlarged ventricles and cortical atrophy. Amyloid-beta plaques, tau tangles, and active microglia surround a damaged neuron, signifying neuroinflammation. Important mechanisms behind memory loss and cognitive decline in AD are also illustrated, including cholinergic neuron degeneration and decreased acetylcholine levels. This figure is created in BioRender

6. Neuroinflammation: The biochemistry of the immune response

6.1. Microglia and inflammatory phenotypes

The study of neuroinflammation entered a new era with the discovery that microglia do not exhibit the simple binary phenotypes M1 (classical activation) and M2 (alternative activation) as previously thought, but rather a wide range of functional states now classified by single-cell RNA sequencing (scRNA-seq). In Alzheimer's disease, the DAM (Disease-Associated Microglia) phenotype stands out, characterized by elevated expression of TREM2, LIPT1, and CTSB, and decreased expression of P2RY12 and CX3CR1. Biochemically, this phenotype secretes a basket of cytokine mediators that can be measured in cerebrospinal fluid and blood [47; 48;49].

6.1.1. Biochemical indicators of neuroinflammation

In Alzheimer's patients, IL-1β levels are elevated in the cerebrospinal fluid (CSF) to between 30 and 80 picograms/ml, compared to less than 10 picograms/ml in healthy individuals. IL-1β activates cyclooxygenase-2 (COX-2) and stimulates the production of prostaglandin E2 (PGE2), which is increased in diseased brain tissue. Tumor necrosis factor-α (TNF-α) levels are also elevated approximately 2-4 times in the CSF, activating the NF-κB pathway, which drives the expression of dozens of inflammatory genes. As for GFAP (Glial Fibrillary Acidic Protein), it is measured in plasma as an indirect indicator of reactive astrogliosis: its plasma value rises from ~100-150 picograms/ml in healthy individuals to 200-400 picograms/ml in patients, and it rises early during the pre-symptomatic phase, making it one of the first biomarkers before the onset of clinical symptoms [50; 51].

6.2. NLRP3 pathway and molecular physiology of inflammasome

The NLRP3 inflammasome complex forms a pivotal biochemical link between amyloid accumulation and neuroinflammation. NLRP3 is activated by two successive stimuli: the priming signal, driven by NF-κB signaling that increases NLRP3 and proIL-1β expression, and the activation signal, given by amyloid crystals via lysosomal destabilization and cathepsin-B leakage into the hyaloplasm, and via an external K^+ efflux in which the intracellular concentration decreases from ~140 to ~80 mmol/L. These signals activate ASC (Apoptosis-associated Speck-like protein) to stimulate speck formation and activate procaspase-1 to active caspase-1 (Caspase-1 p10/p20), which cleaves IL-1β (34 kDa) to active IL-1β (17 kDa) and releases proptosis [52; 53].

7. The coordination chemistry of minerals in Alzheimer's disease

Aβ peptides possess an exceptional ability to bind transition metals via histidine residues (His6, His13, His14) at their amino-terminal ends, forming complexes with alpha-binding capacities (Kd) ranging from 10^{-7} to 10^{-10} mol/L for copper and from 10^{-6} to 10^{-7} mol/L for zinc. Copper accumulation in senescent plaques is estimated at ~390 µmol/L and total zinc at ~1000 µmol/L—more than ten times the physiological concentrations [54].

The biochemical mechanism of copper toxicity is multilevel: Cu^{2+}-Aβ42 stimulates H_2O_2 production at a rate estimated at 0.01–0.1 µmol H_2O_2 per µmol Aβ/min. H_2O_2 is then synergistically produced with Cu^{+} to form highly oxidized HO• radicals (via the Fenton reaction). Zinc controls Aβ aggregation via a histidine-zinc-histidine bridging between Aβ monomers, accelerating oligomer formation. Iron accumulates in dead neurons and fibrillar tangles, stimulating tau oxidation and proliferation. These chemical disturbances are detected by XRF (X-Ray Fluorescence Microscopy) and ICP-MS techniques in postmortem tissue [55; 56].

8. Disruption of cellular signaling pathways

8.1. PI3K/Akt/mTOR pathway and neuroinsulin resistance

Brain insulin resistance reflects a biochemical disruption in a delicate signaling cascade: when Aβ42 peptides bind to the insulin receptor (IR), they stimulate the activation of IKKβ (IκB kinase beta), which phosphorylates IRS-1 at Ser307/Ser612 instead of the normal tyrosine, thus converting IRS-1 from an active mediator to a negative feedback inhibitor of the same insulin receptor. This disrupts the PI3K→PIP3→PDK1→Akt pathway, and conversely, increases the activity of PTEN phosphatase (phosphatase and tensin homolog), which degrades PIP3. This dysfunction is measured in brain tissue by a 2-4-fold increase in the total pSer307-IRS-1/IRS-1 ratio in the hippocampus of Alzheimer's patients [57; 58].

A weakening of the Akt signaling pathway leads to a dangerous chemical reversal: GSK-3β (which Akt inhibits by Ser9 phosphorylation) is activated and directs its destructive phosphorylation toward tau, mTORC1 is inhibited, impairing protein synthesis and synaptic survival, and HIF-1α activity is reduced, decreasing GLUT1/GLUT3 glucose transporter expression and exacerbating cellular energy deficits. This molecular cascade is also revealed in an enzyme network indicator: elevated GSK-3β activity, as measured by direct kinase assay, in postmortem tissues [59].

8.2. Wnt/β-Catenin and maintaining tangles

The Wnt/β-Catenin pathway represents the neuronal synaptic plasticity biochemically. Under normal conditions, the Destruction Complex, composed of APC, Axin, GSK-3β and CK1α, is inhibited after Wnt binds to the Frizzled and LRP5/6 receptors. β-Catenin then accumulates in the hyaloplasm and migrates to the nucleus to activate TCF/LEF genes associated with survival and synapses (including BDNF, Survivin, and Cyclin D1). In Alzheimer's disease, Aβ peptides activate the secretion of DKK1 (Dickkopf-1), which inhibits LRP5/6 and reactivates the destructive complex. β-Catenin is then phosphorylated by GSK-3β at Ser33/Ser37/Thr41 and directed towards ubiquitin-proteasome degradation. The enzyme network results in a 40–60% reduction in nuclear and hyaloplasmic β-Catenin in the hippocampus and prefrontal cortex of Alzheimer's patients [60].

9. Genes and Biochemistry of Risk

9.1. APOE4: From Gene to Chemistry

APOE (Apolipoprotein E — MW ~34 kDa, 299 amino acids) is a cholesterol and phospholipid transporter in the central nervous system. The ε4 allele differs from ε3 at one position: Arg112 instead of Cys112, and from ε2 at two positions (Arg112 and Arg158). These minor structural differences have a significant impact: APOE4 binds to Aβ with a lower affinity than APOE3, reducing its efficiency in preparing Aβ for clearance by LRP1 and microglia. Moreover, intracellular APOE4 is also under proteolytic cleavage, which results in the formation of toxic fragments (APOE4 fragments) with masses of about 25 and 12kDa and accumulates into the hyaloplasm, impairs mitochondrial functions [61; 62].

Biochemically, isoform electrophoresis is used to measure the APOE allele in plasma and APOE is investigated in cerebrospinal fluid by ELISA methods: the concentration of APOE is between 4.5 and 5.5 µg/mL in healthy individuals and it is also different according to the allele. To study the direct molecular interaction of APOE4 and the A2 structure with the A3 structure, modern cryo-EM methods can be employed in instrumental research to reveal small details that were not available before [63].

9.2. TREM2: The molecular guardian of microglia

TREM2 (Triggering Receptor Expressed on Myeloid Cells 2) is a transmembrane protein of type I (MW 230 amino acids, 26 kDa) which has a signaling subunit in common with DAP12. TREM2 interacts with negatively charged phospholipids (PS, PE, LPS), ApoE, and A2, and then triggers the PI3K, Akt, and PLC2 signaling, which transforms microglia into plaque-protective DAM phenotypes. The most examined association with the risk of Alzheimer, R47H mutation in TREM2, is a structural change in the ligand-binding domain that abolishes the affinity by 4-10-folds. The sTREM2 (Soluble TREM2) and insoluble TREM2 are measured using Simoa techniques: in early-middle stages of Alzheimer disease, the sTREM2 in cerebrospinal fluid is increased 30-60-fold over control values, an indication of an intensive microglycoalkyl response [64;65].

10. Biochemistry of synaptic dysfunction

Synaptic dysfunction in Alzheimer's disease unfolds as a stepping biochemical cascade. It begins with the binding of Aβ oligomers to PrPc (Cellular Prion Protein) receptors on the synaptic membrane at an affinity of 10–30 nmol/L, activating the mGluR5 (Metabotropic Glutamate Receptor 5) receptor, which in turn activates Fyn kinase. Fyn phosphorylates the NR2B subunit of the NMDA receptor at Tyr1472, promoting the outflow of Ca^{2+} from the synaptic and activating two synaptic-damaging kinases: calpain and calcineurin. Calcineurin, in turn, activates STEP61 (Striatal-Enriched Protein Tyrosine Phosphatase), which dephosphorylates AMPA receptors and dissociates them from the stabilizing protein PSD-95, leading to receptor internalization and a reduction in synaptic receptor density [66; 67].

At the chemical level, these events translate into a 30–50% decrease in AMPA and NMDA receptor density in the hippocampus during the early to middle stages. This synaptic degeneration is reflected in a recent biochemical marker: the 14-3-3 fragment, physin protein, and SNAP-25 in cerebrospinal fluid (CSF). SYT-1 (Synaptotagmin-1) levels are elevated in CSF during the early stages of the disease and are now considered a preclinical marker of synaptic dysfunction. Neurogranin (NRGN) in CSF is measured using digital photochemical ELISA (Simoa) techniques, increasing from approximately 150–200 pg/mL in healthy individuals to 400–600 pg/mL in Alzheimer's patients, and is a selective marker of dendritic degeneration in the hippocampus [68; 69].

11. Blood-brain barrier dysfunction and NfL index

The blood-brain barrier (BBB) is a crucial biochemical platform, in which the processes of active transport, cell communication, and the inflammatory response are interwoven. The protein levels of proteins regulating tight junction integrity, Claudin-5, Occludin, and ZO-1, are decreased by 20-50 percent in the vessels of Alzheimer patients and augment the permeability of the barrier to the large molecules, which leak out of the neural space. This augmented permeability is watched by rating the albumin quotient (CSF albumin/serum albumin), which is higher than the normal limit of 0.007 in a percentage of patients having Alzheimer disease [70; 71].

In this framework, neurofilament light chain (NfL) a structural axial protein of a mass of about 68 kDa holds a distinct biochemical niche as a biomarker of transboundary axonal degeneration. The level of cerebrospinal fluid (CSF) NfL of normal people of the same age group is about 500-700 pg/mL, whereas in patients with moderate to advanced Alzheimer disease it is about 1000-3000 pg/mL. In large studies, plasma NfL levels, which are relatively low, of about 10-15 pg/mL in healthy individuals and 25-50 pg/mL in patients, correlate with CSF levels, with a correlation coefficient above 0.80, and hence plasma NfL is a good non-invasive alternative. It is also interesting to note that NfL is increased in a broad spectrum of neurodegenerative diseases, which makes it an indicator of degeneration and not an indicator of Alzheimer’s [72; 73].

12. Epigenetic mechanisms and molecular modifications

Epigenetic mechanisms add a dynamic dimension to the stable genetic code: DNA methylation at CpG islands constitutes a stable molecular pattern that is heritable and modifiable by the environment. Extensive changes in methylation patterns have been observed in EWAS (Epigenome-Wide Association Studies): most notably, hypomethylation at the cg05157625 locus in the BIN1 gene and hypermethylation at the ANK1 gene in diseased brain tissue. 5-methyl-cytosine (5mC) and 5-hydroxymethyl-cytosine (5hmC) are measured in postmortem tissue using LC-MS/MS and bisulfite sequencing techniques [74].

At the miRNA level, changes in its expression in cerebrospinal fluid and plasma represent a biochemical window for non-invasively monitoring molecular dysfunction. miR-132-3p—one of the most frequently expressed miRNAs in the hippocampus—is reduced by up to 50% in the brains of Alzheimer's patients compared to healthy individuals; miR-132

regulates PTEN and FOXO3a expression and indirectly modulates tau phosphorylation. Similarly, miR-200b is elevated in the plasma of Alzheimer's patients, and the BACE1 repressor miR-29c is suppressed, contributing to increased BACE1 expression and Aβ production. These epigenetic markers support the overall view that Alzheimer's disease results from an interaction between genetic background, environmental factors, and dynamic molecular alterations [75; 76;77].

13. Conclusion and Future Prospects

The picture of Alzheimer disease presented in this review is a full biochemical portrait of the disease, in which trigger and trigger intertwash in a strictly defined, ascending order. The molecular pathogenesis is characterized by the fact that the molecular secretase system is imbalanced to produce more A2B42 in concentrations more than 500 pg/mL in cerebral fluid, and the A2B42/40 ratio is below 0.10 as the oldest biochemical parameter. The toxic peptides bridge with transition metals (Cu2+, Zn2+, Fe3+) to cause the production of ROS through the Fenton reaction, which is indicated by increased 8-OHdG over 12 nmol/mmol creatinine and increased MDA over 4 nmol/mL. At the same time, A2 peptides change neuronal kinase/phosphatase ratio in favor of active GSK-3- that phosphorylates tau at p -tau181 and p -tau217, elevating plasma levels to diagnostic values. This is augmented by raised plasma GFAP and IL-1b in cerebral spinal fluid, which are indicators of neuroinflammation, and high levels of NfL, a sign of silent axonal degeneration. This is filled in by the genomics: APOE4 dysregulates A2 clearance, TREM2 dysregulates the microglia response, and miRNA changes add to the dysregulation of the BACE1 and tau expression.

The combination of biomarkers into a complex rather than an individual biomarker that is the basis of early diagnosis has three strategic implications: First, the complex of biomarkers should be used as the basis of diagnosis early, not a single biomarker, e.g., high p-tau217 with low A2B40 ratio and high GFAP would be a more specific and selective biomarker signal than either. Second, it should treat the network, not an individual node, a drug targeting BACE1, but without treatment of neuroinflammation and mitochondrial dysfunction will only remove a portion of amyloid and will permit degeneration to proceed. Thirdly, biochemical time is 20 years ahead of clinical time--pre-symptomatic intervention programs are not an add-on, but a treatment requirement.

Scientists are far away: not only multi-targeted medications that treat A, t, and inflammation, but also gene-targeting methods (siRNA and CRISPR) to lower the levels of BACE1 and APOE4, sleep-enhancing lymphatic system, TREM2 pathway, and NLRP3 inflamasome, and artificial intelligence software to analyze proteome, genomic, and epigenome An accurate concept of the biochemistry of Alzheimer disease is in itself no goal, but the key to unlock the day when better treatment becomes available.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests.

References

[1] Engelhardt, E., Resende, E. D. P. F., & Gomes, K. B. (2024). Physiopathological mechanisms underlying Alzheimer's disease: a narrative review. Dementia & Neuropsychologia, 18, e2024VR01. https://doi.org/10.1590/1980-5764-DN-2024-VR01

[2] Haass, C., & Selkoe, D. J. (2007). Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nature reviews Molecular cell biology, 8(2), 101-112. https://doi.org/10.1038/nrm2101

[3] Woodward, M. R., Amrutkar, C. V., Shah, H. C., Benedict, R. H., Rajakrishnan, S., Doody, R. S., ... & Texas Alzheimer Research and Care Consortium. (2017). Validation of olfactory deficit as a biomarker of Alzheimer disease. Neurology: Clinical Practice, 7(1), 5-14. https://doi.org/10.1212/CPJ.0000000000000293

[4] Hampel, Harald, John Hardy, Kaj Blennow, Christopher Chen, George Perry, Seung Hyun Kim, Victor L. Villemagne et al. (2021). The amyloid-β pathway in Alzheimer's disease. Molecular psychiatry 26, no. 10: 5481-5503. https://doi.org/10.1038/s41380-021-01249-0

[5] Twiss, E., McPherson, C., & Weaver, D. F. (2025). Global Diseases Deserve Global Solutions: Alzheimer's Disease. Neurology international, 17(6), 92. https://doi.org/10.3390/neurolint17060092

[6] Xavier, C., & Pinto, N. (2025). Navigating the blurred boundary: Neuropathologic changes versus clinical symptoms in Alzheimer's disease, and its consequences for research in genetics. Journal of Alzheimer's Disease, 104(3), 611-626. https://doi.org/10.1177/13872877251317543

[7] Hajjo, R., Sabbah, D. A., Abusara, O. H., & Al Bawab, A. Q. (2022). A Review of the Recent Advances in Alzheimer's Disease Research and the Utilization of Network Biology Approaches for Prioritizing Diagnostics and Therapeutics. Diagnostics (Basel, Switzerland), 12(12), 2975. https://doi.org/10.3390/diagnostics12122975

[8] Cacabelos R. (2020). Pharmacogenomics of Alzheimer's and Parkinson's diseases. Neuroscience letters, 726, 133807. https://doi.org/10.1016/j.neulet.2018.09.018

[9] Gaugler, J., James, B., Johnson, T., Reimer, J., Solis, M., Weuve, J., ... & Hohman, T. J. (2022). Alzheimer's disease facts and figures. Alzheimers & Dementia, 18(4), 700-789. https://doi.org/10.1002/alz.12638

[10] Sanabria-Castro, A., Alvarado-Echeverría, I., & Monge-Bonilla, C. (2017). Molecular Pathogenesis of Alzheimer's Disease: An Update. Annals of neurosciences, 24(1), 46–54. https://doi.org/10.1159/000464422

[11] Reiss, A. B., Gulkarov, S., Jacob, B., Srivastava, A., Pinkhasov, A., Gomolin, I. H., Stecker, M. M., Wisniewski, T., & De Leon, J. (2024). Mitochondria in Alzheimer's Disease Pathogenesis. Life (Basel, Switzerland), 14(2), 196. https://doi.org/10.3390/life14020196

[12] Choi, S.-B., Kwon, S., Kim, J.-H., Ahn, N.-H., Lee, J.-H., & Yang, S.-H. (2023). The Molecular Mechanisms of Neuroinflammation in Alzheimer's Disease, the Consequence of Neural Cell Death. International Journal of Molecular Sciences, 24(14), 11757. https://doi.org/10.3390/ijms241411757

[13] Engelhardt, E., Resende, E. D. P. F., & Gomes, K. B. (2024). Physiopathological mechanisms underlying Alzheimer's disease: a narrative review. Dementia & Neuropsychologia, 18, e2024VR01. https://doi.org/10.1590/1980-5764-DN-2024-VR01

[14] Nguyen K. V. (2019). β-Amyloid precursor protein (APP) and the human diseases. AIMS neuroscience, 6(4), 273–281. https://doi.org/10.3934/Neuroscience.2019.4.273

[15] Asai, M., Hattori, C., Szabó, B., Sasagawa, N., Maruyama, K., Tanuma, S., & Ishiura, S. (2003). Putative function of ADAM9, ADAM10, and ADAM17 as APP alpha-secretase. Biochemical and biophysical research communications, 301(1), 231–235. https://doi.org/10.1016/s0006-291x(02)02999-6

[16] Dislich, B., & Lichtenthaler, S. F. (2012). The Membrane-Bound Aspartyl Protease BACE1: Molecular and Functional Properties in Alzheimer's Disease and Beyond. Frontiers in physiology, 3, 8. https://doi.org/10.3389/fphys.2012.00008

[17] Selkoe, D.J. (2019). Alzheimer disease and aducanumab: adjusting our approach. Nat Rev Neurol 15, 365–366. https://doi.org/10.1038/s41582-019-0205-1

[18] Busche, M. A., & Hyman, B. T. (2020). Synergy between amyloid-β and tau in Alzheimer's disease. Nature neuroscience, 23(10), 1183–1193. https://doi.org/10.1038/s41593-020-0687-6

[19] Janelidze, S., Stomrud, E., Smith, R., Palmqvist, S., Mattsson, N., Airey, D. C., Proctor, N. K., Chai, X., Shcherbinin, S., Sims, J. R., Triana-Baltzer, G., Theunis, C., Slemmon, R., Mercken, M., Kolb, H., Dage, J. L., & Hansson, O. (2020). Cerebrospinal fluid p-tau217 performs better than p-tau181 as a biomarker of Alzheimer's disease. Nature communications, 11(1), 1683. https://doi.org/10.1038/s41467-020-15436-0

[20] Constantinides, V. C., Paraskevas, G. P., Boufidou, F., Bourbouli, M., Pyrgelis, E. S., Stefanis, L., & Kapaki, E. (2023). CSF Aβ42 and Aβ42/Aβ40 Ratio in Alzheimer's Disease and Frontotemporal Dementias. Diagnostics (Basel, Switzerland), 13(4), 783. https://doi.org/10.3390/diagnostics13040783

[21] Fitzpatrick, A. W. P., Falcon, B., He, S., Murzin, A. G., Murshudov, G., Garringer, H. J., Crowther, R. A., Ghetti, B., Goedert, M., & Scheres, S. H. W. (2017). Cryo-EM structures of tau filaments from Alzheimer's disease. Nature, 547(7662), 185–190. https://doi.org/10.1038/nature23002

[22] Pannuzzo, M. (2022). Beta-amyloid pore linked to controlled calcium influx into the cell: A new paradigm for Alzheimer's Disease. Alzheimer's & Dementia, 18(1), 191-196. https://doi.org/10.1002/alz.12373

[23] Bode, D. C., Baker, M. D., & Viles, J. H. (2017). Ion Channel Formation by Amyloid-β42 Oligomers but Not Amyloid-β40 in Cellular Membranes. The Journal of biological chemistry, 292(4), 1404–1413. https://doi.org/10.1074/jbc.M116.762526

[24] Morito, T., Hashimoto, S., Takamura, R., Watamura, N., Kakiya, N., Fujioka, R., ... & Saido, T. C. (2025). The role of neprilysin and insulin-degrading enzyme in the etiology of sporadic Alzheimer's disease. Journal of Neuroscience, 45(23). https://doi.org/10.1523/JNEUROSCI.2152-24.2025

[25] Hablitz, L. M., & Nedergaard, M. (2021). The glymphatic system: a novel component of fundamental neurobiology. Journal of Neuroscience, 41(37), 7698-7711. https://doi.org/10.1523/JNEUROSCI.0619-21.2021

[26] Wang, Y., & Mandelkow, E. (2016). Tau in physiology and pathology. Nature reviews neuroscience, 17(1), 22-35. https://doi.org/10.1038/nrn.2015.1

[27] Iqbal, K., Liu, F., & Gong, C. X. (2016). Tau and neurodegenerative disease: the story so far. Nature reviews neurology, 12(1), 15-27. https://doi.org/10.1038/nrneurol.2015.225

[28] Medeiros, R., Baglietto-Vargas, D., & LaFerla, F. M. (2011). The role of tau in Alzheimer's disease and related disorders. CNS neuroscience & therapeutics, 17(5), 514–524. https://doi.org/10.1111/j.1755-5949.2010.00177.x

[29] Karikari, T. K., Pascoal, T. A., Ashton, N. J., Janelidze, S., Benedet, A. L., Rodriguez, J. L., ... & Blennow, K. (2020). Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. The Lancet Neurology, 19(5), 422-433. https://doi.org/10.1016/S1474-4422(20)30071-5

[30] Janelidze, S., Berron, D., Smith, R., Strandberg, O., Proctor, N. K., Dage, J. L., ... & Hansson, O. (2021). Associations of plasma phospho-tau217 levels with tau positron emission tomography in early Alzheimer disease. JAMA neurology, 78(2), 149-156. https://doi.org/10.1001/jamaneurol.2020.4201

[31] Barthélemy, N. R., Bateman, R. J., Hirtz, C., Marin, P., Becher, F., Sato, C., ... & Lehmann, S. (2020). Cerebrospinal fluid phospho-tau T217 outperforms T181 as a biomarker for the differential diagnosis of Alzheimer's disease and PET amyloid-positive patient identification. Alzheimer's research & therapy, 12(1), 26. https://doi.org/10.1186/s13195-020-00596-4

[32] Hansson, O. (2021). Biomarkers for neurodegenerative diseases. Nature medicine, 27(6), 954-963. https://doi.org/10.1038/s41591-021-01382-x

[33] Wegmann, S., Eftekharzadeh, B., Tepper, K., Zoltowska, K. M., Bennett, R. E., Dujardin, S., ... & Hyman, B. T. (2018). Tau protein liquid–liquid phase separation can initiate tau aggregation. The EMBO journal, 37(7), EMBJ201798049. https://doi.org/10.15252/embj.201798049

[34] Braak, H., & Del Tredici, K. (2015). The preclinical phase of the pathological process underlying sporadic Alzheimer's disease. Brain, 138(10), 2814-2833. https://doi.org/10.1093/brain/awv236

[35] Hampel, H., Mesulam, M. M., Cuello, A. C., Farlow, M. R., Giacobini, E., Grossberg, G. T., ... & Khachaturian, Z. S. (2018). The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 141(7), 1917-1933. https://doi.org/10.1093/brain/awy132

[36] H Ferreira-Vieira, T., M Guimaraes, I., R Silva, F., & M Ribeiro, F. (2016). Alzheimer's disease: targeting the cholinergic system. Current neuropharmacology, 14(1), 101-115. https://doi.org/10.2174/1570159X13666150716165726

[37] Greig, N. H., Tweedie, D., Rachmany, L., Li, Y., Rubovitch, V., Schreiber, S., ... & Pick, C. G. (2014). Incretin mimetics as pharmacologic tools to elucidate and as a new drug strategy to treat traumatic brain injury. Alzheimer's & Dementia, 10, S62-S75. https://doi.org/10.1016/j.jalz.2013.12.011

[38] Quik, M., Bordia, T., & O'Leary, K. (2007). Nicotinic receptors as CNS targets for Parkinson's disease. Biochemical pharmacology, 74(8), 1224-1234. https://doi.org/10.1016/j.bcp.2007.06.015

[39] Vallés, A. S., & Barrantes, F. J. (2023). Nicotinic Acetylcholine Receptor Dysfunction in Addiction and in Some Neurodegenerative and Neuropsychiatric Diseases. Cells, 12(16), 2051. https://doi.org/10.3390/cells12162051

[40] Butterfield, D. A., & Halliwell, B. (2019). Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nature Reviews Neuroscience, 20(3), 148-160. https://doi.org/10.1038/s41583-019-0132-6

[41] Tönnies, E., & Trushina, E. (2017). Oxidative stress, synaptic dysfunction, and Alzheimer's disease. Journal of Alzheimer's disease, 57(4), 1105-1121. https://doi.org/10.3233/JAD-161088

[42] Mecocci, P., Boccardi, V., Cecchetti, R., Bastiani, P., Scamosci, M., Ruggiero, C., & Baroni, M. (2018). A long journey into aging, brain aging, and Alzheimer's disease following the oxidative stress tracks. Journal of Alzheimer's Disease, 62(3), 1319-1335. https://doi.org/10.3233/JAD-170732

[43] Cenini, G., Lloret, A., & Cascella, R. (2019). Oxidative stress in neurodegenerative diseases: from a mitochondrial point of view. Oxidative medicine and cellular longevity, 2019(1), 2105607. https://doi.org/10.1155/2019/2105607

[44] Swerdlow R. H. (2

[45] 018). Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. Journal of Alzheimer's disease : JAD, 62(3), 1403–1416. https://doi.org/10.3233/JAD-170585

[46] Ali, R. H., Hussein, F. K., Nasar, D. M., & Abd Al salam Salem, A. (2025). The relevance of mitochondrial DNA mutation in human diseases and forensic sciences. Al-Nahrain Journal of Science, 28(1), 96-106. https://dx.doi.org/10.22401/ANJS.28.1.11

[47] Picca, A., Calvani, R., Coelho-Junior, H. J., & Marzetti, E. (2021). Cell Death and Inflammation: The Role of Mitochondria in Health and Disease. Cells, 10(3), 537. https://doi.org/10.3390/cells10030537

[48] Ransohoff R. M. (2016). How neuroinflammation contributes to neurodegeneration. Science (New York, N.Y.), 353(6301), 777–783. https://doi.org/10.1126/science.aag2590

[49] Deczkowska, A., Keren-Shaul, H., Weiner, A., Colonna, M., Schwartz, M., & Amit, I. (2018). Disease-Associated Microglia: A Universal Immune Sensor of Neurodegeneration. Cell, 173(5), 1073–1081. https://doi.org/10.1016/j.cell.2018.05.003

[50] Blennow, K., & Zetterberg, H. (2018). Biomarkers for Alzheimer's disease: current status and prospects for the future. Journal of internal medicine, 284(6), 643–663. https://doi.org/10.1111/joim.12816

[51] Simrén, J., Leuzy, A., Karikari, T. K., Hye, A., Benedet, A. L., Lantero-Rodriguez, J., Mattsson-Carlgren, N., Schöll, M., Mecocci, P., Vellas, B., Tsolaki, M., Kloszewska, I., Soininen, H., Lovestone, S., Aarsland, D., AddNeuroMed consortium, Hansson, O., Rosa-Neto, P., Westman, E., Blennow, K., … Ashton, N. J. (2021). The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. Alzheimer's & dementia: the journal of the Alzheimer's Association, 17(7), 1145–1156. https://doi.org/10.1002/alz.12283

[52] Heneka, M. T., Kummer, M. P., Stutz, A., Delekate, A., Schwartz, S., Vieira-Saecker, A., Griep, A., Axt, D., Remus, A., Tzeng, T. C., Gelpi, E., Halle, A., Korte, M., Latz, E., & Golenbock, D. T. (2013). NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. Nature, 493(7434), 674–678. https://doi.org/10.1038/nature11729

[53] Stancu, I. C., Cremers, N., Vanrusselt, H., Couturier, J., Vanoosthuyse, A., Kessels, S., Lodder, C., Brône, B., Huaux, F., Octave, J. N., Terwel, D., & Dewachter, I. (2019). Aggregated Tau activates NLRP3-ASC inflammasome exacerbating exogenously seeded and non-exogenously seeded Tau pathology in vivo. Acta neuropathologica, 137(4), 599–617. https://doi.org/10.1007/s00401-018-01957-y

[54] Rao, S. S., & Adlard, P. A. (2018). Untangling Tau and Iron: Exploring the Interaction Between Iron and Tau in Neurodegeneration. Frontiers in molecular neuroscience, 11, 276. https://doi.org/10.3389/fnmol.2018.00276

[55] Masaldan, S., Bush, A. I., Devos, D., Rolland, A. S., & Moreau, C. (2019). Striking while the iron is hot: Iron metabolism and ferroptosis in neurodegeneration. Free radical biology & medicine, 133, 221–233. https://doi.org/10.1016/j.freeradbiomed.2018.09.033

[56] Greenough, M. A., Camakaris, J., & Bush, A. I. (2013). Metal dyshomeostasis and oxidative stress in Alzheimer's disease. Neurochemistry international, 62(5), 540–555. https://doi.org/10.1016/j.neuint.2012.08.014

[57] Talbot, K., & Wang, H. Y. (2014). The nature, significance, and glucagon-like peptide-1 analog treatment of brain insulin resistance in Alzheimer's disease. Alzheimer's & dementia : the journal of the Alzheimer's Association, 10(1 Suppl), S12–S25. https://doi.org/10.1016/j.jalz.2013.12.007

[58] de la Monte S. M. (2017). Insulin Resistance and Neurodegeneration: Progress Towards the Development of New Therapeutics for Alzheimer's Disease. Drugs, 77(1), 47–65. https://doi.org/10.1007/s40265-016-0674-0

[59] Inestrosa, N. C., Tapia-Rojas, C., Griffith, T. N., Carvajal, F. J., Benito, M. J., Rivera-Dictter, A., Alvarez, A. R., Serrano, F. G., Hancke, J. L., Burgos, P. V., Parodi, J., & Varela-Nallar, L. (2011). Tetrahydrohyperforin prevents cognitive deficit, Aβ deposition, tau phosphorylation and synaptotoxicity in the APPswe/PSEN1ΔE9 model of Alzheimer's disease: a possible effect on APP processing. Translational psychiatry, 1(7), e20. https://doi.org/10.1038/tp.2011.19

[60] Toledo, E. M., & Inestrosa, N. C. (2010). Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. Molecular psychiatry, 15(3), 272–228. https://doi.org/10.1038/mp.2009.72

[61] Liu, C. C., Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature reviews. Neurology, 9(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

[62] Yamazaki, Y., Zhao, N., Caulfield, T. R., Liu, C. C., & Bu, G. (2019). Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nature reviews. Neurology, 15(9), 501–518. https://doi.org/10.1038/s41582-019-0228-7

[63] Narayan, P., Holmström, K. M., Kim, D. H., Whitcomb, D. J., Wilson, M. R., St George-Hyslop, P., Wood, N. W., Dobson, C. M., Cho, K., Abramov, A. Y., & Klenerman, D. (2014). Rare individual amyloid-β oligomers act on astrocytes to initiate neuronal damage. Biochemistry, 53(15), 2442–2453. https://doi.org/10.1021/bi401606f

[64] Colonna, M., & Wang, Y. (2016). TREM2 variants: new keys to decipher Alzheimer disease pathogenesis. Nature reviews. Neuroscience, 17(4), 201–207. https://doi.org/10.1038/nrn.2016.7

[65] Suárez-Calvet, M., Kleinberger, G., Araque Caballero, M. Á., Brendel, M., Rominger, A., Alcolea, D., Fortea, J., Lleó, A., Blesa, R., Gispert, J. D., Sánchez-Valle, R., Antonell, A., Rami, L., Molinuevo, J. L., Brosseron, F., Traschütz, A., Heneka, M. T., Struyfs, H., Engelborghs, S., Sleegers, K., … Haass, C. (2016). sTREM2 cerebrospinal fluid levels are a potential biomarker for microglia activity in early-stage Alzheimer's disease and associate with neuronal injury markers. EMBO molecular medicine, 8(5), 466–476. https://doi.org/10.15252/emmm.201506123

[66] Selkoe D. J. (2019). Early network dysfunction in Alzheimer's disease. Science (New York, N.Y.), 365(6453), 540–541. https://doi.org/10.1126/science.aay5188

[67] Hynd, M. R., Scott, H. L., & Dodd, P. R. (2004). Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. Neurochemistry international, 45(5), 583–595. https://doi.org/10.1016/j.neuint.2004.03.007

[68] Nilsson, J., Gobom, J., Sjödin, S., Brinkmalm, G., Ashton, N. J., Svensson, J., Johansson, P., Portelius, E., Zetterberg, H., Blennow, K., & Brinkmalm, A. (2021). Cerebrospinal fluid biomarker panel for synaptic dysfunction in Alzheimer's disease. Alzheimer's & dementia (Amsterdam, Netherlands), 13(1), e12179. https://doi.org/10.1002/dad2.12179

[69] Portelius, E., Zetterberg, H., Skillbäck, T., Törnqvist, U., Andreasson, U., Trojanowski, J. Q., Weiner, M. W., Shaw, L. M., Mattsson, N., Blennow, K., & Alzheimer's Disease Neuroimaging Initiative (2015). Cerebrospinal fluid neurogranin: relation to cognition and neurodegeneration in Alzheimer's disease. Brain : a journal of neurology, 138(Pt 11), 3373–3385. https://doi.org/10.1093/brain/awv267

[70] Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nature reviews. Neurology, 14(3), 133–150. https://doi.org/10.1038/nrneurol.2017.188

[71] Nortley, R., Korte, N., Izquierdo, P., Hirunpattarasilp, C., Mishra, A., Jaunmuktane, Z., Kyrargyri, V., Pfeiffer, T., Khennouf, L., Madry, C., Gong, H., Richard-Loendt, A., Huang, W., Saito, T., Saido, T. C., Brandner, S., Sethi, H., & Attwell, D. (2019). Amyloid β oligomers constrict human capillaries in Alzheimer's disease via signaling to pericytes. Science (New York, N.Y.), 365(6450), eaav9518. https://doi.org/10.1126/science.aav9518

[72] Zetterberg, H., & Blennow, K. (2021). Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. Molecular neurodegeneration, 16(1), 10. https://doi.org/10.1186/s13024-021-00430-x

[73] Mattsson-Carlgren, N., Janelidze, S., Palmqvist, S., Cullen, N., Svenningsson, A. L., Strandberg, O., Mengel, D., Walsh, D. M., Stomrud, E., Dage, J. L., & Hansson, O. (2020). Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease. Brain : a journal of neurology, 143(11), 3234–3241. https://doi.org/10.1093/brain/awaa286

[74] Berson, A., Nativio, R., Berger, S. L., & Bonini, N. M. (2018). Epigenetic Regulation in Neurodegenerative Diseases. Trends in neurosciences, 41(9), 587–598. https://doi.org/10.1016/j.tins.2018.05.005

[75] Hébert, S. S., Horré, K., Nicolaï, L., Papadopoulou, A. S., Mandemakers, W., Silahtaroglu, A. N., Kauppinen, S., Delacourte, A., & De Strooper, B. (2008). Loss of microRNA cluster miR-29a/b-1 in sporadic Alzheimer's disease correlates with increased BACE1/beta-secretase expression. Proceedings of the National Academy of Sciences of the United States of America, 105(17), 6415–6420. https://doi.org/10.1073/pnas.0710263105

[76] Patel, N., Hoang, D., Miller, N., Ansaloni, S., Huang, Q., Rogers, J. T., Lee, J. C., & Saunders, A. J. (2008). MicroRNAs can regulate human APP levels. Molecular neurodegeneration, 3, 10. https://doi.org/10.1186/1750-1326-3-10

[77] Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. Lancet (London, England), 397(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4