

Adenosine Receptors in Alzheimer's Disease: A Functional Analysis

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ABSTRACT:

Alzheimer's disease, characterized by a progressive decline in cognitive functions, is one of the most prevalent neurological disorders among the elderly. Adenosine, a purine nucleoside abundant in the central nervous system, serves as a neuroprotective agent. Dysfunction of adenosine receptors plays a critical role in the pathology of Alzheimer's disease and their balance is essential for treating brain disorders. Recently, the role of these receptors in inflammation and apoptosis, key contributors to Alzheimer's disease, has garnered significant attention. This study examines brain development during the embryonic period, identifies brain regions implicated in Alzheimer's disease, and specifically investigates the role of adenosine receptors in this condition. The research employs a descriptive-analytical methodology utilizing library resources.

Keywords: *Alzheimer's disease, adenosine, A1 receptor, A2A receptor.*

1. INTRODUCTION:

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive impairment [1]. Key pathological mechanisms include amyloid-beta accumulation, tau protein hyper phosphorylation, oxidative stress, chronic neuro inflammation, neuronal loss, synaptic dysfunction, aging, and genetic predisposition. AD manifests through diverse symptoms, including memory impairment, challenges in abstract reasoning, behavioral changes, language difficulties, disorientation, emotional instability, and inability to perform routine tasks [2]. These changes often lead to psychological symptoms such as depression, hallucinations, and agitation [3]. Brain imaging comparisons reveal significant atrophy in AD patients, driven by neuronal death and gray matter loss, particularly in the hippocampus, temporal, parietal, and frontal cortices [4]. The hippocampus supports critical cognitive functions, including learning, converting short-term memory to long-term memory, and forming various types of memory. Its excitability enables the transformation of weak stimuli into sustained signals, facilitating memory formation across species. In lower animals, the hippocampus facilitates food selection based on olfactory cues, danger avoidance, responses to sexual pheromones, and critical decision-making. It serves as a hub for decision-making and memory storage for future safety, with mechanisms to convert short-term memory into long-term memory, transforming verbal and symbolic

thinking into accessible information for decision-making. Recent studies have explored the molecular and cellular mechanisms governing hippocampal development, revealing complex interactions among signaling pathways, transcription factors, and environmental factors mediated by various ligands [5]. Adenosine, a neuromodulator in the CNS, regulates synaptic mediators like glutamate, which is essential for learning at physiological levels but neurotoxic in excess [6, 7]. Adenosine receptors, part of the G protein-coupled receptor (GPCR) family, are categorized into A1, A2A, A2B, and A3 subtypes, with A1 and A2A being the most prevalent in the brain [8]. Post-mortem studies indicate altered adenosine receptor distribution and density in AD-affected brain regions, particularly in inflammatory and amyloid/tau-related processes [9]. This study investigates the role of adenosine receptors in AD pathology.

2. THEORETICAL FRAMEWORK:

2.1 Alzheimer's Disease:

Alzheimer's disease is categorized into late-onset and early-onset types. Early-onset, or familial Alzheimer's disease (FAD), typically manifests between ages 30 and 60 and accounts for less than 5% of cases. It results from mutations in the presenilin 1 and presenilin 2 genes on chromosomes 1 and 14 or the amyloid precursor protein (APP) gene on chromosome 21. In contrast, late-onset or sporadic Alzheimer's disease (SAD) is more common and typically appears after age 65 [10]. The role of genetics in Alzheimer's

is not fully elucidated, but researchers have identified genes with significant influence. The apolipoprotein E (APOE) gene significantly influences AD risk, encoding a protein critical for lipid transport, synaptic plasticity, and neuronal repair. It is also involved in neuronal membrane structure, function, and tissue repair, and is naturally expressed in oligodendrocytes, astrocytes, and microglia. In transgenic mice with mutations in APP, presenilin 1, and tau genes, amyloid-beta deposition precedes the pathological effects of neurofibrillary tangles (NFTs). Studies demonstrate that reducing amyloid-beta through immunotherapy prevents tau pathology and mitigates spatial memory deficits [11, 12].

Synaptic dysfunction is a key contributor to memory deficits in Alzheimer's disease. The PSD-95 scaffolding protein, part of the MAGUK family, is located in the postsynaptic region and increases with hippocampal development. It plays a critical role in organizing neurotransmitter signaling factors, adhesion molecules, the cytoskeleton, and glutamate receptors [4]. Alzheimer's prevalence is highest in Asia, accounting for approximately 48% of global cases by 2018, with projections estimating an increase to 59% by 2050, affecting one in 85 people worldwide [13]. In Iran, the Alzheimer's Association reports a rise in cases to 1.5 million, with the highest prevalence in Gilan, Markazi, South Khorasan, and East Azerbaijan provinces. Studies consistently report higher Alzheimer's incidence in women than men, with pathological factors increasing incidence threefold in men and twentyfold in women. Among women, postmenopausal individuals show increased incidence due to reduced neuroprotective estrogen and progesterone levels [14].

The hippocampus is among the first regions affected in Alzheimer's disease. Its embryonic origin involves complex developmental processes beginning in the neural tube and culminating in a highly organized structure. Recent studies have elucidated the molecular and cellular mechanisms governing hippocampal development, revealing intricate interactions among signaling pathways, transcription factors, and environmental factors. The hippocampus originates from the isocortex as part of the fifth limbic lobe on the medial cerebral hemisphere and is considered part of the olfactory cortex. It is connected to the temporal lobe via the fornix fiber tract. During early embryonic development, the hippocampus arises from the medial pallium of the telencephalon, with its primordium specified in the dorsal telencephalon, guided by morphogen gradients such as Wnt and bone morphogenetic proteins (BMPs) [15].

The hippocampus is divided into regions, including the cornu ammonis (CA1–4), dentate gyrus, and subiculum. By embryonic week 9, the hippocampus comprises four layers: a ventricular zone, an intermediate zone, a homogeneous hippocampal plate with bipolar neurons, and a wide marginal zone. By weeks 15–19 of gestation, the hippocampus is

morphologically identifiable [5]. Between weeks 15 and 25, distinct differences in the relative maturity of hippocampal subsections are evident [16]. By weeks 32–34, CA2 and CA3 neurons rapidly enlarge and mature morphologically, surpassing CA1, which still contains some immature neurons. The dentate gyrus develops last, reaching mature cellular structure only after week 34. The cellular structure of hippocampal subregions stabilizes postnatally, though progressive neuronal enlargement and reduced neuronal density occur through childhood and adulthood. Myelination begins perinatally, increases through childhood and adolescence, and stabilizes thereafter [17].

The CA1, CA2, and CA3 regions are central to long-term memory processing. Long-term potentiation (LTP), a form of neural plasticity critical for memory storage, occurs in the hippocampus. The hippocampus is involved in forming explicit (declarative or reflective) long-term memory, encompassing semantic (factual) and episodic (event-based) memory, which is impaired in Alzheimer's disease [18, 19].

The entorhinal cortex (EC), located in the medial temporal lobe, facilitates communication between the hippocampus and neocortex, contributing to memory processing and time perception. The entorhinal-hippocampal system is critical for episodic memory formation, consolidation, and optimization during sleep [20]. In early Alzheimer's, tau protein accumulates in the entorhinal cortex and later spreads to the hippocampus, where plaques and tangles first deposit. Anatomical and histological studies of autopsied Alzheimer's brains indicate that neurodegeneration begins in layer II of the entorhinal cortex, progressively spreading to the hippocampus, temporal cortex, fronto-parietal cortex, and subcortical nuclei. Neurofibrillary tangles initially accumulate in the CA1 region, then progressively deposit in the subiculum, CA2, CA3, and dentate gyrus.

Loss of neuronal populations, particularly glutamatergic neurons in the entorhinal cortex and pyramidal neurons in CA1, is observed in Alzheimer's. CA1 pyramidal neurons are selectively vulnerable to global cerebral ischemia, with pathology severity dependent on ischemia duration [21]. Sirtuins (SIRT), part of the histone deacetylase family, act as intracellular regulatory proteins promoting cell survival. SIRT1 maintains mitochondrial function in neurons and modulates DNA damage responses. Reduced SIRT1 expression in hippocampal neurons impairs cognitive functions, including recent memory and spatial learning. By enhancing mitochondrial biogenesis, activating the SIRT1 pathway may serve as an endogenous neuroprotective mechanism. Amyloid-beta deposition reduces SIRT1 levels, which is critical for neuronal survival, insulin sensitivity, glucose metabolism, and mitochondrial biogenesis, thus maintaining neuronal homeostasis. Recent studies on hippocampal changes in Alzheimer's patients have significant implications for future research and therapeutic strategies [22].

2.2 Adenosine:

Adenosine, a purine nucleoside, is found throughout the body and influences critical neural processes across the brain, affecting normal neurotransmission, learning, memory, motor functions, feeding, sleep, and natural aging [23]. It is a vital mediator of immune responses, with adenosine receptors expressed in various immune cells, regulating immune and inflammatory responses. Their anti-inflammatory effects underscore adenosine's protective role [24, 25]. Adenosine is produced through multiple mechanisms, primarily via de phosphorylation of adenine nucleotides (ATP, ADP, AMP) to adenosine, with ATP as the primary source [26]. Extracellular adenosine is metabolized to inosine by adenosine deaminase or reuptaken via ENT1/ENT2 transporters [27].

2.3 Types of Adenosine Receptors:

Many of adenosine's immunomodulatory effects in the CNS are mediated by A1 and A2A receptors, though recent evidence suggests involvement of A2B and A3 receptors. All four adenosine receptor subtypes are expressed in astrocytes, oligodendrocytes, and microglia [28]. A1 and A3 receptors inhibit adenylate cyclase activity via Gi/o proteins, reducing cAMP formation, while A2A and A2B receptors stimulate adenylate cyclase via Gs proteins, increasing cAMP levels [8].

A1 receptors, highly expressed in the cortex, hippocampus, and glial cells, regulate neurotransmitter release, sleep, pain, and neuroprotection [29, 30]. Presynaptically, A1R activation inhibits adenylate cyclase, reducing cyclic adenosine-3,5-monophosphate (cAMP) and regulating cAMP-dependent protein kinase activity. Additionally, A1R activates phospholipase C, modulating phosphatidylinositol metabolism and increasing inositol 1,4,5-triphosphate (IP3) and diacylglycerol levels. IP3 stimulates Ca²⁺ release from intracellular stores and inhibits N-, Q-, and P-type calcium channels, reducing Ca²⁺ influx, glutamate release, and neuronal excitability [30]. Postsynaptically, A1R activation opens potassium channels, increasing K⁺ efflux, hyperpolarizing the membrane, and reducing excitability, thereby promoting neuroprotection. A1R also opens ATP-sensitive potassium channels in substantia nigra neurons, increasing outward currents and reducing membrane excitability [31].

A2A receptor expression occurs both centrally and peripherally, with the highest levels in dopamine-rich brain regions (e.g., striatum, globus pallidus, nucleus accumbens, olfactory tubercle) and immune system, and lower levels in the cortex, hippocampus, heart, lungs, and blood vessels. A2A receptors are expressed in pre- and postsynaptic neurons, astrocytes, microglia, and oligodendrocytes, coordinating functions such as glutamate release, excitotoxicity, glial responses, blood-brain barrier permeability, and peripheral

immune cell migration [8]. At high adenosine levels, A2A receptor binding predominates, reducing A1 receptor activation. This activates a specific neuronal Gs protein subtype (Golf), triggering the AC/cAMP/PKA cascade and increasing GABA uptake [32]. Studies in Alzheimer's rat models show that A2A receptor inhibition improves memory deficits and long-term hippocampal inhibition caused by tau hyperphosphorylation, normalizes the glutamate/GABA ratio, reduces inflammatory markers, and enhances LTP in CA3 pyramidal cells [8].

2.4 Adenosine and Its Changes in Alzheimer's:

Evidence suggests that A1 and A2A receptors are linked to neurodegenerative disorders like Alzheimer's, Huntington's, Parkinson's, and other dementias, playing critical roles in modulating neuroinflammation [33, 34]. In Alzheimer's pathogenesis, adenosine receptor balance is disrupted, primarily manifesting as reduced A1R expression and increased A2AR expression, leading to impaired inhibitory and excitatory processes and cognitive dysfunction. Restoring this balance by activating A1 receptors and inhibiting A2A receptors may enhance cholinergic system function, hippocampal synaptic plasticity, and neurotrophic factors, providing neuroprotection [9].

A1 receptors appear neuroprotective, while A2A receptors contribute to neurodegeneration [7]. In the hippocampus, high A1 receptor expression allows adenosine to exert inhibitory effects, modulating learning and memory through LTP and long-term depression (LTD) [35]. Limited reports address A1 receptor roles in Alzheimer's. For instance, a 2020 study showed that 28-day A1 agonist administration improved spatial memory in Alzheimer's animal models [36]. Conversely, Craig Vollert et al. (2013) found that chronic A1 receptor antagonist treatment in aged APPswe/PS1dE9 mice failed to improve memory, instead reducing exploratory behavior and worsening long-term memory [37]. A1 receptor activation via PKC and ERK1/2 pathways increases soluble APP α production and, due to its role in amyloid-beta metabolism, A1 agonists may be effective for Alzheimer's treatment, even in advanced stages [34].

Chronic caffeine consumption (a non-selective adenosine receptor antagonist) prevents amyloid-beta plaque formation and associated cognitive deficits in Alzheimer's mouse models. A2AR antagonists, such as caffeine, improve memory deficits, suggesting A2AR blockade as an effective strategy for memory enhancement [9].

2.5 Alzheimer's, Inflammation, and Adenosine:

Inflammation is a complex process involving immune cells and soluble mediators to protect organisms from harmful stimuli like infections, damaged cells, or irritants. It is also a significant component of pathological conditions, including rheumatic diseases,

neurological disorders, and cancer [2]. Chronic, uncontrolled CNS inflammation is a recognized pathological factor in neurological and neuropsychiatric disorders, including Alzheimer's, Parkinson's, Huntington's, and multiple sclerosis, characterized by glial cell activation, proinflammatory cytokine and chemokine production (e.g., IL-1 β), increased blood-brain barrier permeability, peripheral immune cell infiltration, neuronal damage, death, and atrophy over time [38, 39,40]. Protein deposition and excessive immune cell activation impair neuronal structure and function, leading to episodic memory loss and cognitive impairment, hallmark Alzheimer's symptoms [41].

Modulation of neuroinflammation by adenosine receptors makes them attractive therapeutic targets for neurodegenerative diseases with chronic brain inflammation, including Alzheimer's [20]. A2A receptors promote proinflammatory functions in the CNS, particularly influencing microglia during inflammation and neurodegeneration, driving microglia toward a proinflammatory phenotype. A2A receptors induce microglial proliferation [42], and their inhibition prevents neuroinflammation in the hippocampus, mitigates IL-1 β -induced toxicity, and suppresses microglial responses, protecting neurons [8]. Conversely, A1 receptors exhibit anti-inflammatory effects, reducing proinflammatory cytokines [43]. A 2020 study by Aleix Martí Navia et al. confirmed A1 receptors' anti-inflammatory and neuroprotective roles, while A2A receptors promoted neuroinflammation [44].

2.6 Alzheimer's, Apoptosis, and Adenosine:

Apoptosis, or programmed cell death, is a natural process essential for maintaining tissue health and balance. It is critical in nervous system development but is inappropriately activated in Alzheimer's, causing excessive neuronal loss in brain regions responsible for learning and memory consolidation, such as the hippocampus and cortex [45]. Alzheimer's-related proteins, including amyloid-beta and tau, induce apoptosis. Amyloid-beta triggers oxidative stress, mitochondrial dysfunction, and increased caspase-3 (a key apoptosis mediator), while hyperphosphorylated tau destabilizes microtubules and impairs intracellular transport, leading to apoptosis [8, 24]. Chronic inflammation also significantly contributes to apoptosis [7, 24].

Adenosine receptors influence both the induction and prevention of apoptosis. A2A receptors can induce or inhibit apoptosis depending on cell type, physiological conditions, and adenosine concentration. A2A activation may increase pro-apoptotic protein expression (e.g., Bax), forming mitochondrial pores, releasing cytochrome c, and activating caspases. A study on A2A receptor deficiency in hippocampal cells of mice exposed to chronic hypoxic-hypercapnic conditions showed reduced apoptosis, decreased p38 MAPK activation, reduced Bax mRNA expression,

and increased Bcl-2 mRNA expression [46]. A2AR antagonists exhibit antioxidant and anti-apoptotic activities, reducing amyloid-beta levels by decreasing genes involved in APP cleavage [9]. Nelson Rebola et al. (2018) found that A2A antagonist SCH58261 prevented p38 and JNK phosphorylation and caspase activation [47]. Conversely, A1 receptors have anti-apoptotic effects, activating the PI3K/Akt pathway, which promotes cell survival by phosphorylating and inactivating pro-apoptotic proteins like BAD. A1 receptors also inhibit caspases (e.g., caspase-3), increase anti-apoptotic protein expression (e.g., Bcl-2), and suppress stress pathways like JNK, preventing apoptosis [48, 49].

Previous studies showed that A1R and A2AR regulate the cAMP-PKA-CREB signaling pathway with opposing effects [8]. Exploring interactions between these receptors could provide comprehensive insights into their roles in inflammation and apoptosis.

3. LITERATURE REVIEW:

Marucci et al. (2021) demonstrated that A1AR agonists (CCPA) and A2AAR antagonists (ZM241385) reduced cytokine-induced neuroinflammation (e.g., TNF- α , IL-1 β , IFN- γ) in microglial cells [50].

Meads et al. (2021) showed A1AR agonists protected against memory deficits in soman-induced epilepsy. Passive avoidance memory tests showed that CPA-treated rats exhibited more avoidance behaviors than the diseased group, suggesting A1AR agonists as a promising neuroprotective strategy to prevent long-term learning and memory impairments [51].

In 2019, Carvalho et al. reported that increased A2A receptor expression exacerbated tau hyperphosphorylation and memory deficits in THY-22 mice, paving the way for novel therapeutic approaches [52].

Martire et al. (2019) investigated the neuroprotective effects of partial A1 receptor agonists (2-dCCPA, 3-dCCPA) in cerebral ischemia. Electrophysiological tests on 12-week-old C57Bl/6 mice and open-field tests at 16 weeks confirmed A1 receptors' neuroprotective role, suggesting partial A1 agonists for ischemia treatment [53].

Mouro et al. (2019) examined A2A receptor antagonists (Istradefylline, SCH58261) in preventing memory deficits from chronic cannabinoid exposure, showing improved memory in the Novel Object Recognition test and enhanced synaptic plasticity [54].

Huiming Ren et al. (2019) found that A2A receptor deficiency in hippocampal cells of mice under chronic hypoxic-hypercapnic conditions inhibited apoptosis, reducing p38 MAPK activation, Bax mRNA expression, and increasing Bcl-2 mRNA expression [46].

Nelson Rebola et al. (2018) showed that intraventricular SCH58261 injection prevented hippocampal LTP changes from intraperitoneal LPS-induced microglial activation and neuroinflammation,

inhibiting P38 and JNK phosphorylation, caspase activation, and reducing IL-1 α and IL-1 β levels, suggesting A2A antagonists for inflammatory and neurodegenerative diseases like Alzheimer's [47].

Additional studies (2013–2018) consistently support A1 agonists and A2A antagonists for neuroprotection and memory improvement [55–61].

4. CONCLUSION:

Alzheimer's disease, a leading cause of dementia, affects millions globally, with projections of 131.5 million cases by 2050 [4]. Pathological hallmarks include amyloid-beta, tau, inflammation, and apoptosis [1]. In AD, A1 receptor expression decreases in the hippocampus, while A2A receptor expression increases, disrupting cognitive function [8]. A1 activation and A2A inhibition mitigate excitotoxicity, inflammation, and apoptosis, enhancing memory and neuroprotection. A2A antagonists (e.g., caffeine, SCH58261) and A1 agonists (e.g., CPA) show therapeutic promise [51,54]. Given the extensive interactions between A1 and A2A receptors in neurons, such as opposing effects on glutamate release and coupling to different G protein subunits, further investigation into their roles and mechanisms could significantly advance memory improvement and neuroprotection in Alzheimer's. Currently, no definitive Alzheimer's treatment exists. Pharmacological treatments, such as cholinesterase inhibitors (e.g., Exelon), and non-pharmacological interventions (e.g., music or occupational therapy) manage symptoms but may cause side effects like nausea, vomiting, diarrhea, or reduced appetite. Deeper investigation into signaling pathways, stem cell therapies, lifestyle changes, and increased awareness, particularly in individuals with a positive family history, could pave the way for effective treatments.

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