REVIEW ARTICLE

P2X7 Receptor Signaling in Alzheimer's Disease: A Critical Review of Mechanisms and Emerging

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Abstract

Alzheimer's disease (AD) is one of the most common causes of age-related memory impairment, progressively eroding an individual's ability to retain personal memories, recognize familiar faces, and engage with daily life, while posing a substantial and growing burden on global healthcare systems. Extensive research has established that chronic neuroinflammation and neurodegenerative processes are central to AD pathophysiology, with increasing attention focused on the purinergic P2X7 receptor (P2X7R). This ligand-gated ion channel is markedly upregulated in AD and is implicated in multiple pathological events, including amyloid-β plaque accumulation, neurofibrillary tangle formation, microglial activation, excessive production of reactive oxygen species, and sustained inflammatory signaling. Through these interconnected mechanisms, P2X7R contributes to neuronal injury and progressive cognitive decline. Due to its central involvement in converging disease pathways, P2X7R has emerged as a promising therapeutic target. This review synthesizes current evidence on the role of P2X7R in AD pathogenesis and highlights emerging pharmacological strategies aimed at modulating this receptor, offering potential avenues for slowing disease progression and improving therapeutic outcomes in individuals with AD.

Key words: Alzheimer's disease, amyloid-β pathology, neuroinflammation, P2X7 receptor, therapeutic targets

INTRODUCTION

Alzheimer's disease (AD) exerts a profound impact not only on affected individuals but also on families and society, progressively impairing memory, adaptive capacity, and social relationships. With rapid population aging, particularly in China, where the number of individuals aged over 60 years is projected to reach nearly 500 million by 2050, the prevalence of AD is expected to rise sharply, intensifying social, economic, and healthcare challenges. In the absence of effective preventive or disease-modifying therapies, AD threatens fundamental aspects of daily functioning and quality of life.[1] Conventionally, AD has been characterized by extracellular deposition of amyloid-β (Aβ) plaques and intracellular aggregation of hyperphosphorylated tau protein. However, these hallmark features alone fail to fully account for disease onset, progression, or clinical heterogeneity.[2] Increasing evidence highlights additional pathological processes, including synaptic loss, chronic neuroinflammation, mitochondrial dysfunction, and excessive production of reactive oxygen species (ROS), all of which contribute to neuronal injury and cognitive decline. Notably, mitochondrial abnormalities and oxidative stress can occur independently of Aβ plaques and tau tangles, underscoring the multifactorial and complex nature of AD pathogenesis.[3,4] Despite significant advances in understanding disease mechanisms, accurate diagnosis of AD remains challenging, and currently available therapies offer only modest symptomatic relief or limited slowing of disease progression.[5-9] Given the involvement of multiple, interconnected pathological pathways, there is growing interest in identifying novel therapeutic targets

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beyond the classical amyloid- and tau-centered paradigms. One such emerging focus is the purinergic signaling system, particularly the P2X7R. P2X7R is a ligand-gated ion channel widely expressed in neural and glial cells, where it acts as a key regulator of inflammatory and stress-related responses. Under pathological conditions, sustained activation of P2X7R can trigger a cascade of detrimental events, including enhanced oxidative stress, abnormal tau modification, increased Aβ accumulation, and prolonged neuroinflammatory signaling. Through these converging mechanisms, P2X7R occupies a central position in the neurodegenerative processes underlying AD and represents an attractive target for therapeutic intervention aimed at delaying or halting disease progression.[10] Beyond AD, P2X7R has been implicated in a range of neurological disorders, including Parkinson's disease, multiple sclerosis, and Huntington's disease, where its activation exacerbates disease severity and symptom burden. These findings emphasize the broader pathological relevance of P2X7R across neurodegenerative and neuroinflammatory conditions.[11] Importantly, experimental studies using J20 transgenic mouse models have demonstrated that pharmacological inhibition of P2X7R significantly reduces Aβ plaque burden. Such interventions also attenuate tau pathology and oxidative damage, further reinforcing the close association between P2X7R signaling and key molecular features of AD. Collectively, these observations suggest that P2X7R is not merely a downstream contributor but a pivotal driver of disease progression and a promising target for next-generation therapeutic strategies.[12] In this review, we summarize the molecular characteristics, structural features, and functional properties of P2X7R. We then examine its role in the pathogenesis of AD, followed by a discussion of our key findings and recent advances in the development of P2X7R antagonists as potential therapeutic agents.[13]

P2X7R: Molecular structure and functional mechanisms

Adenosine 5'-triphosphate (ATP), widely recognized as the primary intracellular energy source, also functions as a critical neurotransmitter within the nervous system.[14] Since the initial identification of purinergic receptors in 1976, research has revealed multiple subtypes, including seven P2X and eight P2Y receptors.[15] Among these, the P2X purinoceptors comprise the ionotropic P2X7R. Similar to other P2X receptors, P2X7R forms an ATP-gated, non-selective homotrimeric cation channel, but it exhibits distinct structural and functional features that set it apart from other family members. All P2X receptors (P2X1–7) assemble as homotrimers, composed of three identical subunits.[16]

The P2X7R is characterized by two transmembrane domains, a cysteine-rich extracellular loop, and an unusually long intracellular C-terminal tail compared to other P2X receptors. Each subunit has been likened to a "jumping dolphin," and together, the trimer forms a cup-shaped structure.[16] Unlike other purinergic receptors, P2X7R requires much higher concentrations of ATP for activation, generally in the millimolar range. On brief ATP stimulation, it functions as a non-selective cation channel, permitting K^+ efflux and Ca^{2+}/Na^+ influx, thereby inducing inward currents and membrane depolarization.[17] Prolonged activation of P2X7R can trigger the formation of a large pore, allowing the passage of molecules larger than typical ions. This process initiates downstream events such as inflammatory cytokine release, membrane remodeling, and, in some cases, cell death.[18-20] While the precise molecular mechanism of pore formation remains debated, two primary hypotheses have emerged. One suggests that the channel itself gradually dilates over time, supported by observations that small fluorescent dyes (~1.4 nm) can permeate the expanding pore.[21] The alternative theory implicates recruitment of the pannexin-1 hemichannel, as deficiency of pannexin-1 significantly reduces dye uptake in astrocytes, although contradictory findings exist.[34] A potential explanation for these discrepancies is that different P2X7R splice variants may vary in their pore-forming capabilities.[22-24]

P2X7R FUNCTIONS: CENTRAL NERVOUS SYSTEM

P2X7R in microglia

The P2X7R, initially characterized in immune cells, plays a key role in regulating microglial function. Activation of P2X7R enhances microglial migration and phagocytic activity, processes that depend on glycogen synthase kinase-3 (GSK3). Accordingly, pharmacological inhibition of P2X7R reduces Aβ plaque burden in the rat hippocampus, an effect linked to suppression of GSK3 signaling in microglia.[25] Supporting these findings, post-mortem AD brain samples and transgenic mouse models consistently show elevated P2X7R expression in microglia localized around amyloid plaques.[26] In addition, P2X7R activation drives microglial proliferation and promotes the release of pro-inflammatory cytokines, particularly interleukin-1β, underscoring its central role in microglial activation and neuroinflammation.

P2X7R expression in neurons

Early studies reported strong P2X7R immunoreactivity in excitatory nerve terminals, and *in situ* hybridization revealed P2X7R mRNA in NeuN-positive neurons. During neurodevelopment, P2X7R is expressed in neuronal precursors and neuroblastoma cells, and useful P2X7R is found in human stem cells, stem cell-derived neuronal cells, and neural precursor cells from both developing and adult mouse brain regions. However, some immunohistochemical studies detect P2X7R only on neural precursor cells and microglia, but not on mature neurons. Despite these discrepancies, functional evidence indicates that P2X7R

influences neuronal processes. It regulates axonal growth and alkaline phosphatase, acting downstream of P2X7R, and modulates axon development. Introducing ATP to cultured hippocampal neurons delays axon extension, whereas P2X7R antagonism or genetic deletion enhances axonal growth and branching. P2X7R also modulates neurotransmitter release at the presynaptic terminal and contributes to neuronal differentiation. Under pathological conditions, however, P2X7R becomes detrimental. It mediates ATP-induced neuronal death, as selective P2X7R antagonists (A438079, KN-62) prevent ATP-triggered neurotoxicity in pure cultures.[27] Elevated P2X7R activity has also been directly linked to increased ATP-induced neuronal death.[28]

P2X7R expression and function in both oligodendrocytes and astrocytes

P2X7R is not just in microglia; it is also present in astrocytes and oligodendrocytes.[29] In astrocytes, the P2X7R acts like a key communication hub, helping these glial cells stay actively involved in shaping brain activity. When this receptor is activated, it can influence the release of glutamate – one of the brain's primary neurotransmitters – thereby affecting how neurons and glial cells talk to each other. It also regulates ATP release, which then triggers calcium waves that travel across networks of astrocytes. These slow, coordinated calcium signals allow astrocytes to "share information" over long distances, supporting the brain's intricate web of cellular communication. P2X7R is not just important for astrocytes. Its activation ramps up the production of MCP-1/CCL2 through pathways like p38 MAPK and ERK1/2, highlighting its role in astrocyte-driven inflammation. The receptor is also functionally relevant in Schwann cells and oligodendrocytes, where its expression increases after injury. Interestingly, studies using EGFP reporter mice have even visualized P2X7R activity in oligodendrocytes in P2X7 BAC transgenic models, offering direct evidence of its broader involvement in glial physiology. Other findings even suggest that P2X7R may help oligodendrocytes move or reposition themselves during disease, pointing to its broader involvement in neurodegenerative processes.

Relationship and functional interactions between P2X7R and AB

The accumulation of Aβ as extracellular plaques is a hallmark of AD, formed when amyloid precursor protein (APP) is cleaved by specific aspartic proteases through amyloidogenic or non-amyloidogenic pathways. In the amyloidogenic pathway, APP is cleaved by β- and γ-secretases to produce Aβ fragments, while in the non-amyloidogenic pathway, α- and γ-secretases generate soluble APP-α and p3 fragments, with sAPP-α having neuroprotective roles. Both pathways operate within the same central nervous system cell types, and current research seeks to understand how the balance shifts toward excessive Aβ accumulation in AD. Multiple signaling pathways shape how amyloid-β (Aβ) is produced, but GSK-3β stands out as a key driver. When GSK-3β activity rises, Aβ generation tends to increase. Fascinatingly, studies in J20 transgenic mice show that blocking the P2X7R can reduce Aβ buildup and boost α-secretase activity, most likely by dampening GSK-3β signaling. Beyond this, GSK-3β also influences how APP is processed: it affects presenilin-1 (PS1) function, which in turn alters γ-secretase activity, and it works with nuclear factor-κB to raise β-secretase (BACE1) expression. Together, these interactions place GSK-3β at the center of several critical steps in Alzheimer's pathology. When this delicate balance is disturbed, the result is an overproduction of Aβ, fueling the harmful processes that drive AD. By blocking the P2X7R, antagonists help ease these harmful effects. They work by dialing down GSK-3β activity, which in turn lowers the buildup of Aβ, offering a potential path to slowing Alzheimer's progression.[14] Beyond its role in APP processing, the P2X7R also shapes how microglia behave. When activated, it encourages microglia to move toward senile plaques and affects their ability to clear Aβ. Supporting this, studies show that treatment with the P2X7R antagonist Brilliant Blue G reduces plaque buildup in AD animal models, underscoring the receptor's influence on microglial responses and disease progression. Repeated studies show that using the P2X7R antagonist Brilliant Blue G helps reduce the buildup of amyloid plaques in AD animal models, pointing to its potential as a therapeutic strategy.

RELATIONSHIP BETWEEN P2X7R ACTIVITY AND TAU DYSREGULATION

One of the hallmarks of AD is the formation of neurofibrillary tangles and clumps made up largely of tau protein that has become excessively phosphorylated and twisted out of its normal shape. Tau normally stabilizes microtubules and supports axonal structure by binding polymerized tubulin. In AD, tau becomes excessively phosphorylated, detaches from microtubules, and forms NFTs, disrupting neurons. This abnormal phosphorylation is driven by kinases such as GSK-3β, CDK5, protein kinase A, and protein kinase C, with GSK-3β being the most studied, acting largely through the PI3K/AKT pathway. Activation of the P2X7R promotes tau phosphorylation via GSK-3β. Inflammation worsens tau accumulation, and reducing microglial activation can help. Levels of the P2X7R are found to be higher in the brains of patients with tau-related disorders and in mouse models of these conditions. Strikingly, when the receptor is removed, both synaptic plasticity and memory improve, pointing to its critical role in disease progression. Likewise, the P2X7R antagonist GSK1482160 enhances cognitive performance in tauopathy mice.[30] Inflammatory signals also play a part in disrupting tau regulation. When interleukin (IL)-1β activity becomes excessive, it drives tau pathology forward. By contrast, blocking IL-1β helps to slow this process, reducing the buildup of tau in the brain.[31] In the P301S mouse model, microglia become activated before tau tangles appear,

speeding up both disease progression and behavioral decline. These reactive microglia also help spread tau abnormalities across the brain. Remarkably, blocking the P2X7R in P301S mice reduces tau buildup and improves cognitive function, likely by curbing tau release through exosomes. Further studies show that P2X7R antagonists can rebalance phosphorylated tau inside and outside neurons, which helps protect against cell death.[32] In addition, blocking P2X7R lowers the levels of tissue-non-specific alkaline phosphatase (TNAP) – an enzyme that drives tau phosphorylation outside cells. By reducing TNAP activity, P2X7R suppression helps ease tau-related damage and further limits the progression of pathology.[33]

P2X7R and neuroinflammatory mechanisms in AD

Neuroinflammation is now understood as the third major hallmark of AD, playing a critical role in both how the disease begins and how it advances. What makes this idea especially important is that it connects the two dominant theories of Alzheimer's – the amyloid hypothesis and the tau hypothesis – into a unified picture of disease progression. At the center of this process are microglia, the brain's resident immune cells, which act as key regulators of inflammation within the nervous system.[34] Microglia act as the brain's frontline guardians, sensing and responding to injury while keeping the immune system in balance and controlling inflammation. Depending on the signals they receive from their surroundings, they can shift into different roles – either becoming M1 cells that drive inflammation, or M2 cells that calm inflammation and help repair tissue.[35] M1 microglia act as powerful amplifiers of brain inflammation by releasing cytokines such as tumor necrosis factor-alpha, IL-1β, IL-6, and IL-18. Among these, IL-1β plays a central role in driving microglia-mediated inflammatory responses. Its production and release are tightly controlled by the NLRP3 inflammasome, which switches on when microglia are stimulated. The P2X7R is a key player in this process – it helps activate NLRP3 and enables the conversion of IL-1β from its inactive precursor into its mature, active form. This happens in two steps: First, cells build up pro-IL-1β inside, and then caspase-1 cleaves it into active IL-1β. Importantly, even when large amounts of the precursor are present, IL-1β secretion still depends on P2X7R activation,[36] highlighting the receptor's essential role in cytokine regulation. When the P2X7R is activated, it causes potassium (K^+) to flow out of the cell – a crucial signal that sparks the assembly of the NLRP3 inflammasome. These complex forms, when NLRP3 links up with the adaptor protein ASC, which then brings in pro-caspase-1. Once activated, caspase-1 cuts the inactive precursors pro-IL-1β and pro-IL-18 into their active forms, allowing these inflammatory molecules to be released.[37] Interestingly, when NLRP3 activity is disrupted, Aβ deposits are reduced in APP/PS1 Alzheimer's models. This finding highlights the NLRP3/caspase-1 pathway as a promising therapeutic target for slowing or managing AD.

The role of P2X7R in mitochondrial dysfunction during AD

In the earliest stages of AD, the brain begins to undergo subtle but important changes – marked by inflammation, protein buildup, and early signs of neuronal dysfunction. One of the most striking shifts is in energy metabolism: Glucose use in the brain drops, a phenomenon known as glucose hypometabolism. This is often detected with FDG-PET scans and points to mitochondrial dysfunction as a major driver of disease progression. Research increasingly links the P2X7R to problems in the cell's recycling systems. For example, P2X7R has been tied to impaired microglial autophagy in amyotrophic lateral sclerosis, and its activation disrupts lysosomal function. Mitochondrial health is normally kept in balance by AMPK, a key regulator of mitochondrial fission. When P2X7R is activated, it triggers mitochondrial fission and mitophagy through AMPK, but in Alzheimer's, this process goes awry. Instead of maintaining a healthy turnover of mitochondria, the system breaks down, leading to oxidative damage, reduced energy production, and cognitive decline. Oxidative stress plays a central role here. It arises when ROS, natural by-products of metabolism, overwhelm the cell's antioxidant defences. While ROS normally serve useful physiological functions, their excessive buildup is strongly linked to Alzheimer's pathology. In fact, high levels of isoprostane 8,12-iso-iPF(2α) -VI, a marker of lipid peroxidation, have been found in the urine, plasma, and cerebrospinal fluid of people with mild cognitive impairment. This suggests that oxidative imbalance appears very early, even before the brain shows significant plaque or tangle formation. Increased ROS levels are similarly found across various neurodegenerative illnesses, and AD patients commonly display higher protein oxidative indicators such as protein carbonyls and 3-nitrotyrosine. Mitochondrial dysfunction, a major source of ROS, increases oxidative damage, another hallmark of AD. Recent findings indicate that P2X7R is also localized within mitochondria. Loss of mitochondrial P2X7R alters basal and ATP-linked respiration, maximal respiratory capacity, mitochondrial membrane potential, and matrix Ca^{2+} levels, demonstrating its essential role in mitochondrial energy homeostasis. In addition, AD brains exhibit reduced proteasome activity, and chronic P2X7R activation has been shown to impair the ubiquitin–proteasome system, ultimately contributing to the death of neurons.[38] Collectively, these observations suggest that P2X7R influences multiple metabolic pathways central to AD pathophysiology. Furthermore, P2X7R activation in APPswe/PS1dE9 AD mice model might trigger neuronal harm by generating ROS.[39] Another study also revealed that Aβ can cause mitochondrial toxicity, although the presence of P2X7R in microglial cells is needed. Moreover, ATP can activate P2X7R in the cell membrane of microglia, leading to the formation of hydrogen peroxide. Presently, P2X7R activation follows stimulation with BzATP or ATP, which may encourage macrophages and microglia to generate ROS. The researchers also discovered that P2X7R inhibitors reduced

ROS production. Mitochondria malfunction and oxidative stress seem like key factors in the beginning of illness.

P2X7R as therapeutic target in AD

Deposition of amyloid, tau hyperphosphorylation, chronic neuroinflammation, and oxidative stress are among the major pathogenic mechanisms implicated in AD, which is gradually recognized as a complex neurodegenerative disorder. Importantly, P2X7R participates in each of these processes, often exerting a substantial influence during the earliest stages of disease development. Its antagonistic behavior under high ATP concentrations makes P2X7R an appealing therapeutic target, as pharmacological inhibition does not interfere with its physiological functions at lower ATP levels. *In vivo* studies have shown that P2X7R suppression reduces amyloid plaque burden, providing early evidence that P2X7R antagonists may be effective in AD treatment. Similarly, giving P2X7R antagonists to AD mice can prevent amyloid plaque formation, and removing P2X7R genetically improves cognitive function in APP/PS1 mice. Extensive research further supports P2X7R as a promising therapeutic target, demonstrating reduced pathological hallmarks and neurological impairments in AD animal models following either pharmacological blockade or genetic ablation of the receptor. The P2X7R blocker BBG has been shown to improve learning, spatial memory, and overall cognitive performance in AD mouse models. BBG, derived from the food-safe dye Brilliant Blue FCF, is non-toxic in healthy animals and approved for consumption in the U.S. under names like FD&C Blue No. 1 or Acid Blue 9. Importantly, BBG also has a better ability to cross the blood–brain barrier. Beyond reducing purinoceptor expression, BBG has been found to inhibit gliosis in the brain. Furthermore, while BZ-ATP treatment increases IL-1β release in Aβ (1–42)-primed human microglia, pre-treatment with a P2X7R antagonist effectively counteracts this response. In addition to direct antagonism, therapeutic strategies may also involve targeting downstream components of the P2X7R signaling pathway. Taken together, these findings underscore the considerable therapeutic potential of P2X7R modulation in AD.

ADVANCES IN DRUG RESEARCH

P2X7R has been known as a prospective therapeutic aim for several diseases, including neurodevelopmental disorders.[40] Notably, P2X7R antagonists have exhibited substantial potential in treating multiple sclerosis and ALS, mostly due to their neuroprotective actions inside the central nervous. The P2X7R agonist BzATP is known to trigger pore formation, release of IL-1β, and calcium influx in rat, mouse, and human receptors. Over the years, numerous P2X7R antagonists have been investigated, and extensive studies have documented species-dependent variations in receptor responses to these compounds. Although recent research has advanced the development of brain-penetrant P2X7R antagonists, most available compounds have poor blood–brain barrier permeability, limiting their effectiveness in live studies. The majority of identified drugs have limited blood–brain barrier permeability, which limits their usefulness in *in vivo* research, despite recent efforts to identify brain-penetrant P2X7R antagonists. Among the substances with proven CNS access, GlaxoSmithKline's GSK1482160 exhibits robust brain penetration. Similarly, the amide drug GSK1370319A demonstrates great CNS entrance and has been demonstrated to prevent inflammasome-mediated cell death and neuronal degeneration.

P2X7R as a new diagnostic approach for AD

PET imaging has been widely used for detecting neurological disorders, including AD In addition to supporting diagnosis, PET techniques can reveal disease subtypes based on underlying pathology or, in some cases, genetic factors, thereby aiding therapeutic decision-making. Historically, PET studies in AD have relied heavily on the radiotracer [^18F] FDG to measure alterations in brain glucose metabolism. Over time, however, a broad range of radiotracers has been developed to interrogate specific molecular targets, including several that bind to P2X7R. Among these, ^11C-JNJ-54173717, a high-affinity P2X7R antagonist, has demonstrated strong utility as a PET radioligand, enabling *in vivo* mapping of P2X7R expression, including selective imaging in non-human primates. Another tracer, ^18F-JNJ64413739, has shown reliability for visualizing P2X7R in the human brain and offers a promising tool for assessing P2X7R-focused therapies in both AD patients and healthy subjects. Although additional studies with larger cohorts are required to determine whether P2X7R-targeted PET imaging can stratify AD by severity, current findings suggest substantial potential for this approach. The P2X7R isn't confined to the brain. It's also found on peripheral immune cells such as T lymphocytes and macrophages. Interestingly, higher levels of P2X7R have been detected in the blood of people with AD, suggesting that circulating P2X7R might help distinguish patients from healthy individuals. Although no single biomarker should be relied upon for diagnosis, combining plasma P2X7R with other markers could improve accuracy and provide a stronger tool for identifying Alzheimer's.

CONCLUSION

The progression of AD, characterized by Aβ accumulation and tau pathology, is closely associated with aberrant P2X7R activity. Suppression of P2X7R signaling has been shown to improve cognitive performance and reduce tau pathology in experimental models of tauopathy. In AD animal models, pharmacological P2X7R antagonists, including GSK1482160 and Brilliant Blue G, demonstrate beneficial effects by attenuating amyloid plaque deposition, dampening

neuroinflammatory responses, and preserving memory and cognitive function. These findings highlight P2X7R as a key modulator of convergent pathological pathways in AD. Although the complex and context-dependent nature of P2X7R signaling presents therapeutic challenges, its ability to influence both amyloid- and tau-driven mechanisms underscores its promise as a disease-modifying target. Collectively, current evidence supports P2X7R modulation as a viable strategy for the development of novel therapeutic interventions aimed at slowing AD progression.

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