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Purinergic Receptors as Potential Therapeutic Targets in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive loss of memory and cognitive ability and is a serious cause of mortality. Many of the pathological characteristics associated with AD are revealed post-mortem, including amyloid- β plaque deposition, neurofibrillary tangles containing hyperphosphorylated tau proteins and neuronal loss in the hippocampus and cortex. Although several genetic mutations and risk factors have been associated with the disease, the causes remain poorly understood. Study of disease-initiating mechanisms and AD progression in humans is inherently difficult as most available tissue specimens are from late-stages of disease. Therefore, AD researchers rely on *in vitro* studies and the use of AD animal models where neuroinflammation has been shown to be a major characteristic of AD. Purinergic receptors are a diverse family of proteins consisting of P1 adenosine receptors and P2 nucleotide receptors for ATP, UTP and their metabolites. This family of receptors has been shown to regulate a wide range of physiological and pathophysiological processes, including neuroinflammation, and may contribute to the pathogenesis of neurodegenerative diseases like Parkinson's disease, multiple sclerosis and AD. Experimental evidence from human AD tissue has suggested that purinergic receptors may play a role in AD progression and studies using selective purinergic receptor agonists and antagonists *in vitro* and in AD animal models have demonstrated that purinergic receptors represent novel therapeutic targets for the treatment of AD.

Keywords

Alzheimer's disease; Neuroinflammation; P2Y Receptor; P2X Receptor; P1 receptor

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1. Introduction

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by global cognitive decline, including progressive loss of memory, orientation, reasoning and functional abilities. It is predicted that AD prevalence will grow rapidly in the United States with an estimated 13.8 million AD patients by the year 2050, almost triple the 4.7 million patients in 2010 (Hebert et al., 2013). The associated care required will present unprecedented challenges to the health care system (Hebert et al., 2013). The causes of AD are not well understood and many of the pathological characteristics of the AD brain are revealed postmortem, including β -amyloid plaque deposition, hyperphosphorylated tau tangle formation and degeneration of neurons in the hippocampus and the neocortex (Butterfield and Boyd-Kimball, 2004; Hurtado et al., 2010; Obulesu et al., 2011). A primary hallmark of AD is the production of the amyloid- β_{1-42} peptide (A β) that results from the sequential processing of amyloid precursor protein (APP) by β - and γ -secretases resulting in a buildup of neurotoxic A β peptide and eventual plaque deposition and neurodegeneration (O'Brien and Wong, 2011). Several genetic mutations within the APP processing pathway have been shown to cause early-onset AD, namely mutations in APP itself or in the γ -secretase subunits presenilin-1 (PS1) and presenilin-2, although these mutations represent less than 5% of all AD cases (Lemere et al., 1996; Campion et al., 1999; O'Brien and Wong, 2011). The vast majority of AD patients develop late-onset AD with no known genetic cause, although several risk-factor genes have been identified, including the *apoE4* allele of apolipoprotein. Individuals that inherit one copy of *apoE4* have a 30% lifetime risk of developing AD by the age of 85 while those with 2 copies of *apoE4* have a 60% lifetime risk (Genin et al., 2011). How exactly the *apoE4* gene allele contributes to the pathogenesis of AD is still not well understood.

Although methods to prevent or reverse AD are not available, it is predicted that a treatment that merely slows the progression of the disease could dramatically reduce the number of AD patients in the coming years (Hebert et al., 2013). Current FDA-approved treatments for AD include two classes of drugs: acetylcholinesterase inhibitors that prevent the breakdown of the neurotransmitter acetylcholine to improve cognition and NMDA receptor antagonists that reduce glutamate-induced neuronal excitotoxicity (Cummings, 2004; Huang and Mucke, 2012). Clinical improvement of AD symptoms using these drugs is modest and neither drug can prevent or reverse disease pathology (Cummings, 2004; Huang and Mucke, 2012). Several novel therapeutic strategies for AD are currently being pursued, including decreasing production or increasing clearance of the amyloidogenic A β peptide, preventing tau phosphorylation and aggregation, and administration of anti-inflammatory agents (Cummings, 2004; Cole and Frautschy, 2010; Huang and Mucke, 2012). Unfortunately, these therapeutic strategies have been ineffective and in some cases cause undesirable side effects (Scharf et al., 1999; Aisen et al., 2000; Aisen et al., 2003; Gilman et al., 2005; Green et al., 2009; Salloway et al., 2009; Schor, 2011). The absence of effective treatments to retard the progression of AD strongly encourages attempts to identify initiating mechanisms that could potentially serve as therapeutic targets.

Because the majority of available human AD tissue samples are from deceased patients in the late-stages of disease, investigating the initiating cellular mechanisms and the

progression of AD pathologies in humans is difficult. Furthermore, the inability to perform mechanistic studies using live cells and tissues makes most studies of human samples primarily correlative (Kalaria et al., 1990; Ulas et al., 1993; Angulo et al., 2003; Lai et al., 2008). As a result, AD researchers have relied heavily upon the use of transgenic AD-like mouse models and *in vitro* studies of brain tissue from these mice to investigate the initiating mechanisms of AD. Findings with these approaches have revealed that inflammation is a major characteristic of AD that is manifested by the increased accumulation of cytokines, *e.g.*, IL-1 β , TNF- α and IFN- γ (Chakfe et al., 2002; Suzuki et al., 2004), the enhanced activation of microglial cells and astrocytes (Frautschy et al., 1998; Schlachetzki and Hull, 2009; Simpson et al., 2010) and production of neurotoxic forms of A β (D'Andrea et al., 2001; Hardy and Selkoe, 2002; Nagele et al., 2003; Butterfield and Boyd-Kimball, 2004; Willuweit et al., 2009). Although it is clear that neuroinflammation is a major component of AD (Heppner et al., 2015), its role in disease pathogenesis is less clear as it could be a response to A β accumulation and neurodegeneration, a primary driver of AD progression or an early protective response (Wyss-Coray, 2006). Early in AD progression, inflammation may be neuroprotective, as acute activation of resident immune cells (*i.e.*, microglia) by inflammatory molecules can increase the clearance of neurotoxic A β and dead neurons to help maintain brain homeostasis and synapse stability (Koizumi et al., 2007; Kim et al., 2012). Alternatively, chronic inflammation within the brain can enhance reactive gliosis and the production of damaging reactive oxygen species (ROS) that directly contribute to neurodegeneration (Parvathenani et al., 2003; Pekny et al., 2014). Identifying anti-neuroinflammatory drugs and the ideal stage of disease for their administration could lead to novel treatments for AD.

Purinergic signaling through P1 receptors for adenosine and P2 receptors for adenosine 5'-triphosphate (ATP), uridine 5'-triphosphate (UTP) and their metabolites is now recognized as playing a prominent role in the modulation of many physiological processes, including immune cell recruitment, inflammation, neurotransmission, regulation of vascular and muscle tone and perception of pain (Di Virgilio, 1998; Abbracchio and Ceruti, 2007; Trautmann, 2009; Tsuda et al., 2009; Burnstock, 2010; Stagg and Smyth, 2010; Bours et al., 2011). P1 and P2 receptor subtypes are expressed throughout the nervous system where they have been shown to play a role in Parkinson's disease, Huntington's disease and multiple sclerosis (Popoli et al., 2002; Chen and Brosnan, 2006; Pinna, 2014; Burnstock, 2015), making these receptors attractive drug targets for novel therapies to treat AD. To date, there have been no human clinical trials undertaken to investigate the therapeutic potential of targeting specific purinergic receptors to treat AD, although a recently-announced Phase II clinical trial will determine the therapeutic effectiveness of intravenous ATP infusion on cerebral metabolism and mental state in patients with moderate to severe AD ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02279511): NCT02279511). The therapeutic potential of purinergic receptors in other human inflammatory and neurodegenerative diseases has already been recognized, as a number of clinical trials have investigated their role in the treatment of rheumatoid arthritis, inflammatory bowel disease, cancer and Parkinson's disease (Agteresch et al., 2000; Villalona-Calero et al., 2008; Beijer et al., 2010; Arulkumaran et al., 2011; Hauser et al., 2014). The role of purinergic receptors in neuroinflammation, neurodegeneration and CNS disorders has been extensively reviewed. (Apolloni et al., 2009; Burnstock et al., 2011;

Weisman et al., 2012b; Weisman et al., 2012c; Burnstock, 2015). Here, we focus on the relevance of recent studies on purinergic signaling to potential therapies for Alzheimer's disease, with an emphasis on findings with human samples and studies in which selective agonists and antagonists for P1 and P2 receptor subtypes have been investigated *in vitro* and in mouse models of AD.

2. P1 receptors in AD

P1 adenosine receptors are a family of seven transmembrane domain G protein-coupled receptors ranging from 318–412 amino acids with 4 subtypes having been identified: A₁, A_{2A}, A_{2B} and A₃ receptors (Pirainen et al., 2011). These receptors can further be classified according to their preferred G protein interaction, where A₁ and A₃ receptors primarily couple to G_i protein leading to inhibition of adenylyl cyclase and decreased cyclic adenosine 5'-monophosphate (cAMP) levels, whereas A_{2A} and A_{2B} receptors primarily signal through G_s protein leading to activation of adenylyl cyclase and increased cAMP production, although coupling of each P1 receptor subtype to other G proteins has been described (Fredholm et al., 2001). Within the central nervous system (CNS), P1 receptors have been shown to play a role in a number of neurodegenerative diseases, including AD, making them potential therapeutic targets (Schwarzschild et al., 2006; Rahman, 2009; Stone et al., 2009; Rivera-Oliver and Diaz-Rios, 2014).

Although there exists sufficient evidence to suggest that A_{2B} and A₃ receptors represent therapeutic targets in the CNS (Rosi et al., 2003; Chen et al., 2006; Popoli and Pepponi, 2012; Little et al., 2015), A₁ and A_{2A} receptor antagonism has been the most well studied therapeutic approach involving P1 receptors and neurological disorders. In Parkinson's Disease (PD), A_{2A} receptors are thought to contribute to disease pathologies through modulation of dopaminergic signaling, where A_{2A} receptors decrease the binding affinity of dopamine to D2 receptors (Diaz-Cabiale et al., 2001; Morelli et al., 2010). Furthermore, studies in human PD patients have shown A_{2A} receptors to be upregulated in the brain regions affected by PD and increased A_{2A} receptor expression is an early event in disease progression (Mishina et al., 2011; Villar-Menendez et al., 2014). A_{2A} receptor antagonists, including Istradefylline (KW-6002), Preladenant (SCH420814) and Tozadenant (SYN115), have undergone Phase I-III clinical trials with varying degrees of success in the treatment of Parkinson's Disease (LeWitt et al., 2008; Hauser et al., 2011; Hauser et al., 2014; Pinna, 2014). Interestingly, the most widely consumed drug in the world, caffeine (Fredholm et al., 1999), is an A₁ and A_{2A} receptor antagonist and a Phase III clinical trial is currently underway to assess caffeine administration as an effective therapy for Parkinson's Disease ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01738178): NCT01738178). Several epidemiological studies in humans also have demonstrated the beneficial cognitive effects of caffeine consumption that have been associated with a lower risk of developing PD, AD and dementia (Ascherio et al., 2001; Maia and de Mendonca, 2002; Eskelinen and Kivipelto, 2010) and reduced age-related cognitive decline (van Gelder et al., 2007). While the contributions of A₁ and A_{2A} receptors to the development and progression of AD in humans are unknown, the expression of these receptors is altered in areas of the brain known to be involved in the progression of the disease. Previous studies using post-mortem brain samples from AD patients and age-matched controls have shown decreased A₁ receptor expression in both the dentate gyrus

and CA3 regions of the hippocampus of AD patients, focal points for the spread of AD-associated neurofibrillary tangles and neuronal loss (Braak and Braak, 1996), which was attributed to neuronal cell death in these brain regions (Jansen et al., 1990; Kalaria et al., 1990; Ulas et al., 1993). In contrast, another study utilized post-mortem AD frontal cortex samples and showed increased expression of A₁ and A_{2A} receptors, as compared to the frontal cortex of age-matched control patients (Albasanz et al., 2008). Yet another study using AD patient samples and age-matched controls found that expression of A₁ receptors was increased in degenerating neurons and around A β plaques in the AD brain, whereas A_{2A} receptor expression, which was found primarily in neurons of the striatum in control patients, was increased in glial cells of the cortex and hippocampus of AD patients (Angulo et al., 2003). Taken together, these studies provide evidence of P1 receptor contributions to AD-related pathologies and suggest that the expression and distribution of these receptors in the AD brain is region- and cell type-specific.

Unlike studies and clinical trials with A₁ and A_{2A} receptor antagonists or agonists for the treatment of Parkinson's disease, investigations of their potential as therapeutic agents in Alzheimer's disease have been limited to *in vitro* studies and the use of animal models of AD. In the SH-SY5Y human neuroblastoma cell line, it has been shown that activation of the A₁ receptor (A₁R) using the selective agonist (*R*)-N⁶-(1-methyl-2-phenylethyl)adenosine (R-PIA) can enhance soluble APP α (sAPP α) production through a PKC- and ERK1/2-dependent mechanism suggesting that activation of the A₁R is neuroprotective by promoting α -secretase-mediated non-amyloidogenic sAPP α production (Angulo et al., 2003). A₁R-mediated sAPP α production was further shown to be attenuated by the selective A₁R antagonist dipropylcyclopentylxanthine (DPCPX) (Angulo et al., 2003). Additionally, the neuroprotective effects of caffeine have been demonstrated in cultured rat cerebellar neurons where its application reduced A β -induced neurotoxicity primarily through A_{2A} receptor (A_{2A}R) antagonism, as addition of the selective A_{2A}R antagonist ZM241385 mirrored the neuroprotective effects of caffeine whereas the selective A₁R antagonist 8-cyclopentyltheophylline (CPT) had no effect (Dall'Igna et al., 2003). Caffeine has also been shown to produce neuroprotective effects *in vivo* in transgenic AD mouse models expressing mutant forms of APP and/or PS1. Administration of caffeine to transgenic mice expressing the Swedish mutant of APP (APP^{swe}) beginning at 4 months of age through 8 months of age was shown to protect against cognitive decline in a battery of behavioral tests, as well as reduce the levels of neurotoxic A β ₁₋₄₂ in the hippocampus (Arendash et al., 2006). Although the exact mechanism of caffeine-mediated neuroprotection was unclear, *in vitro* release of A β ₁₋₄₀ and A β ₁₋₄₂ was decreased in a dose-dependent manner following caffeine addition to differentiated N2a neuronal cells, suggesting that antagonism of neuronal A₁Rs and/or A_{2A}Rs and decreased amyloidogenic A β production is neuroprotective (Arendash et al., 2006). In the APP^{swe} and APP+PS1 mouse models of AD, short-term caffeine treatment (< 24 h) reduced plasma A β levels in both ~3 month-old mice (before A β plaque development in the brain) and 15~20 month-old mice (after A β plaque development) (Cao et al., 2009). Furthermore, long-term caffeine treatment (4 weeks) in ~18 month-old APP^{swe} mice was shown to reduce A β plaque load in the brain and reverse cognitive declines (Cao et al., 2009). In the intracerebroventricular (ICV) A β injection mouse model, which demonstrates A β -induced cognitive impairment and neurotoxicity, both caffeine and the selective A_{2A}R

antagonist SCH58261 were shown to prevent A β -induced cognitive impairments (Dall'Igna et al., 2007) and SCH58261 was further shown to reduce synapse loss and hippocampal neuron toxicity following ICV A β administration in rats (Canas et al., 2009). Pharmacological A_{2A}R blockade also attenuated A β -induced neuronal death in rat primary cultured neurons, likely through a reduction in A_{2A}R-mediated p38 MAPK activation and preservation of hippocampal synaptosome function (Canas et al., 2009). Interestingly, while these studies have primarily targeted A₁ and A_{2A} receptor antagonism in the brain as a therapeutic modality, it has been shown that A₁ and A_{2A} receptor agonism using NECA (5'-*N*-ethylcarboxamidoadenosine; a pan-P1 receptor agonist) or the FDA-approved A_{2A}R agonist Lexiscan (regadenoson) increases the permeability of the blood-brain barrier to macromolecules, including anti-A β antibodies, in the APP^{swe}/PS1^{dE9} mouse model of AD (Carman et al., 2011). This effect was thought to be mediated through adenosine receptor signaling in brain endothelial cells that make up part of the blood-brain barrier. These findings suggest that NECA and Lexiscan could be used as a combination therapy with other drugs to increase brain penetrance and improve the likelihood of drugs reaching their intended target within the brain. The results of these studies further suggest that P1 receptors, specifically A₁ and A_{2A} adenosine receptors, may represent novel drug targets for the treatment of AD.

3. P2 receptors in Alzheimer's disease

3.1. P2X receptors in Alzheimer's disease

P2X receptors (P2XR) are a family of ATP-gated cation channels ranging in size from 379–595 amino acids in length and consisting of intracellular N- and C-termini, two transmembrane domains and a large extracellular loop that shares ~33% sequence homology between the seven P2X receptor subtypes (P2X1–7) and contains a putative consensus ATP-binding site (Vial et al., 2004; Weisman et al., 2012b). P2X receptor subtypes interact in a number of homotrimeric and heterotrimeric configurations to regulate a variety of physiological and pathophysiological processes in the CNS, including pain sensation, neurotransmitter release and neuroinflammation (Rodrigues et al., 2005; Khakh and North, 2006; Koles et al., 2007; Ulmann et al., 2008). The expression of P2X receptor subtypes in the CNS varies with brain region and cell type, with P2X2, P2X4 and P2X6 receptors being highly expressed in neurons where their activation has been shown to induce both pre- and post-synaptic responses (Tanaka et al., 1996; Kanjhan et al., 1999; Rubio and Soto, 2001; Watano et al., 2004; Rodrigues et al., 2005; Khakh and North, 2006). Although P2X receptor subtypes are widely expressed in the CNS in both neurons and glial cells (Khakh and North, 2006; Illes et al., 2012), the role of most P2X receptor subtypes in CNS pathologies is not clearly defined. However, one prominent functional role for P2X receptors is the regulation of pain sensation, particularly by the P2X3 receptor and P2X2/P2X3 receptor heterotrimers in neurons and P2X4 receptors in microglia (Chizh and Illes, 2001; Tsuda et al., 2003; Ford, 2012). Blockade of P2X3 and P2X2/3 receptors by local application of the selective antagonist A-317491 has been shown to attenuate both chronic inflammatory pain and thermal neuropathic pain in mice, suggesting that P2X3 and P2X2/3 receptor antagonists may represent novel analgesics (Jarvis et al., 2002; McGaraughty et al., 2003). The therapeutic relevance of P2X3 and P2X2/3 receptor blockade, as well as blockade of other

P2X receptor subtypes, has not been investigated in the context of Alzheimer's disease, except in the case of the P2X7 receptor.

Among the P2X receptors, the P2X7 receptor (P2X7R) has garnered the most attention due to its key role in the regulation of inflammatory responses in a number of pathophysiological circumstances, including bacterial infection, lung inflammation, salivary gland inflammation and neuroinflammation (Monif et al., 2009; Lucattelli et al., 2011; Weisman et al., 2012b; Woods et al., 2012; Csoka et al., 2015). High concentrations of extracellular ATP (> 0.1 mM), such as those observed under inflammatory conditions (Cauwels et al., 2014), are required for P2X7R activation, likely because the fully ionized form of ATP (*i.e.*, ATP⁴⁻) is the primary agonist (Steinberg et al., 1987). P2X7R activation leads to the opening of non-selective cation channels whose sustained activity induces mitochondrial and plasma membrane depolarization, the formation of plasma membrane pores, plasma membrane blebbing, and production of reactive oxygen species (Weisman et al., 1984; Parvathenani et al., 2003; Verhoef et al., 2003; Lister et al., 2007; Roger et al., 2008; Lee et al., 2011). One of the primary roles of the P2X7R is in immune cells where its activation stimulates the formation and activation of the NLRP3 inflammasome leading to increased caspase-1 activity and subsequent processing and release of IL-1 β , a cytokine whose levels are elevated in the AD brain (Di Virgilio, 2007; Simi et al., 2007; Shaftelet et al., 2008; Woods et al., 2012). P2X7R activation also has been shown to increase the release of TNF- α , IL-18 and IL-6, as well as induce apoptotic cell death, making the P2X7R an attractive therapeutic target to reduce inflammation and ATP-induced apoptosis through P2X7R antagonism (Hide et al., 2000; Perregaux et al., 2000; Kong et al., 2005; Shieh et al., 2014). In fact, human clinical trials have been undertaken to investigate the therapeutic potential of P2X7R antagonists in inflammatory diseases, including rheumatoid arthritis, Crohn's disease and chronic obstructive pulmonary disease (Arulkumaran et al., 2011). Although there is clinical interest in testing P2X7R antagonism as a therapy for human CNS disorders (Chrovian et al., 2014), no clinical trials to date have specifically targeted the P2X7R in the CNS. Therefore, evidence for the role of the P2X7R in AD has primarily come from *in vitro* studies and the use of animal models of AD.

The P2X7R is widely distributed in the CNS and its expression has been reported in neurons, astrocytes and microglia where P2X7R activation contributes to numerous physiological processes, including neurotransmitter release from neurons and intercellular crosstalk via Ca²⁺ signaling (Collo et al., 1997; Verderio and Matteoli, 2001; Sperlagh et al., 2002; Sperlagh et al., 2006). P2X7R also contributes to CNS pathologies where its antagonism has been shown to be therapeutic in mouse models of neurodegeneration and neuroinflammation, including ischemia, Huntington's disease, multiple sclerosis and AD (Matute et al., 2007; Diaz-Hernandez et al., 2009; Chu et al., 2012; Diaz-Hernandez et al., 2012). Because microglia are primary drivers of neuroinflammation, antagonism of microglial P2X7Rs may reduce neuroinflammatory responses in the AD brain that have been shown to contribute to disease pathogenesis (Heppner et al., 2015). Exposure of both human and rodent microglia to A β has been shown to increase P2X7R expression (McLarnon et al., 2006) and induce the release of proinflammatory cytokines, including TNF α , IL-6 and IL-1 β (Yates et al., 2000; Combs et al., 2001; Parajuli et al., 2013), whose levels have been shown to be elevated in the brains of human AD patients and in mouse models of AD (Griffin et al.,

1989; Patel et al., 2005; Simi et al., 2007; Sanz et al., 2009). The P2X7R appears to play a prominent role in the regulation of IL-1 β levels in the brain, as intrahippocampal A β injection causes a large accumulation of IL-1 β in the hippocampi of wild type, but not P2X7R^{-/-} mice (Sanz et al., 2009). The lack of A β -induced IL-1 β accumulation in P2X7R^{-/-} mouse hippocampus is likely due to the loss of microglial P2X7Rs, as *in vitro* studies have shown that A β increases ATP release, [Ca²⁺]_i, and IL-1 β release from primary microglia of wild type, but not P2X7R^{-/-} mice, suggesting that microglial P2X7Rs are a primary regulator of inflammation in the AD brain (Sanz et al., 2009). In the human AD brain, P2X7R expression has been shown to colocalize with activated microglia surrounding A β plaques and, in microglia isolated posthumously from AD patients, P2X7R expression was shown to be significantly increased compared to microglia from non-demented patients (McLarnon et al., 2006). Similarly, the P2X7R was shown to be upregulated in both the Tg2576 and APPswe/PS1dE9 transgenic mouse models of AD and its expression colocalized with microglia surrounding A β plaques (Parvathenani et al., 2003; Lee et al., 2011). Furthermore, P2X7R activation by ATP or the high affinity P2X7R agonist BzATP (3'-O-(4-benzoyl)benzoyl-ATP) (Erb et al., 1990) significantly enhanced ROS production in primary rat microglia, and P2X7R-expressing microglia in APPswe/PS1dE9 mice exhibited significant ROS production that colocalized with decreased expression of the synapse protein postsynaptic density-95 (PSD-95), suggesting that P2X7R-mediated ROS production by microglia cells contributes to synaptic loss in this mouse model of AD (Parvathenani et al., 2003; Lee et al., 2011). Microglial P2X7R upregulation was also observed in a rat model where A β ₁₋₄₂ was directly injected into the hippocampus, which lead to memory deficits and degeneration of hippocampal neurons within 7 days (Kowall et al., 1991; Malin et al., 2001; McLarnon et al., 2006). Administration of the selective P2X7R antagonist Brilliant Blue G (BBG) (Jiang et al., 2000) following hippocampal A β ₁₋₄₂ injection was shown to confer neuroprotection and reduce inflammatory responses, reactive gliosis and neuronal loss in the hippocampus (Ryu and McLarnon, 2008). In a similar mouse model, BBG administration following intrahippocampal A β injection significantly decreased A β -induced cognitive deficits. However, neuronal P2X7Rs appear to contribute to A β -induced neurodegeneration in mice, since *in vitro* studies using primary hippocampal neurons demonstrated that blockade of neuronal P2X7Rs by BBG attenuated A β -induced loss of dendritic spines and filopodia (Chen et al., 2014). Similarly, neuronal P2X7R antagonism was shown to be therapeutic in the J20 hAPP transgenic mouse model of AD where systemic BBG administration prevented the formation of A β plaques (Diaz-Hernandez et al., 2012). It was demonstrated that inhibition of the P2X7R by BBG increased α -secretase activity in hippocampal neurons via glycogen synthase kinase 3-beta (GSK-3 β), thus reducing the generation of A β and subsequent plaques, although decreased IL-1 β accumulation in the hippocampus was also observed following BBG administration, suggesting that blockade of microglial P2X7R is also therapeutic in this model (Diaz-Hernandez et al., 2012). Beneficial effects of P2X7R antagonism also may result from blockade of P2X7R-mediated apoptosis, as neuronal P2X7R activation by ATP or BzATP has previously been shown to induce caspase- and FAS-mediated apoptosis (Kong et al., 2005; Gandelman et al., 2013).

Lastly, there is some evidence that the P2X4 receptor (P2X4R) may contribute to neurodegeneration in Alzheimer's disease. It has been demonstrated that treatment of rat primary hippocampal neurons with the neurotoxic A β ₁₋₄₂ peptide increases P2X4R expression and cell death (Varma et al., 2009). Furthermore, increasing P2X4R expression through lentiviral-based transfection led to increased A β ₁₋₄₂-induced neuronal death, whereas decreasing P2X4R expression using P2X4R siRNA decreased A β -induced neuronal death (Varma et al., 2009). Neuronal death caused by A β was postulated to result from dysregulation of P2X4R-mediated Ca²⁺ influx whereby A β enhanced caspase 3-mediated cleavage of the P2X4R C-terminus thus increasing Ca²⁺ channel closure time and decreasing agonist-dependent receptor internalization from the cell membrane. As previous studies have already demonstrated that A β induces the release of the P2XR agonist ATP from microglia (Kim et al., 2007; Kim et al., 2012), it is suggested that increased A β levels in the AD brain enhance ATP release from microglia to increase P2X4R activation leading to neuronal cell death. Interestingly, P2X4R expression was shown to be downregulated in the frontal lobe of AD patients with severe cognitive impairment, as compared to non-diseased control patients, where it was hypothesized that A β -induced P2X4R expression increased neuronal death (Varma et al., 2009). The observed decrease in P2X4R expression in the AD brain may be indicative of the loss of P2X4R-expressing neurons in late-stage AD. These findings suggest that, in addition to the P2X7R, the P2X4R may represent a novel therapeutic target for the treatment of AD.

3.2. P2Y receptors in Alzheimer's disease

P2Y receptors (P2YRs) are a family of classical seven transmembrane spanning G protein-coupled receptors with extracellular N-termini containing potential glycosylation sites and structurally diverse intracellular domains that couple with G_q, G_s or G_i proteins (Erb et al., 1995; Flores et al., 2005; Abbracchio et al., 2006; Burnstock, 2015). Eight different P2Y receptor subtypes (P2Y₁, P2Y₂, P2Y₄, P2Y₆, P2Y₁₁₋₁₄) ranging from 328 to 377 amino acids have been cloned and characterized as having distinct pharmacological profiles in their response to endogenous agonists, including ATP, UTP, adenosine 5'-diphosphate (ADP), uridine 5'-diphosphate (UDP) and UDP-glucose (Abbracchio et al., 2006; Burnstock, 2006). Several positively charged amino acids that are conserved among the P2YR subtypes have been shown to facilitate the binding of fully ionized, negatively charged P2Y₂R agonists to the receptor (Lustig et al., 1992; Erb et al., 1995). P2Y₁, P2Y₂, P2Y₄, P2Y₆ and P2Y₁₁ receptors are coupled to the heterotrimeric G_q protein whose activation stimulates phospholipase C (PLC) and subsequent inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol generation leading to release of Ca²⁺ from intracellular stores and activation of protein kinase C (PKC), respectively (Abbracchio et al., 2006). The P2Y₁₁ receptor also couples to G_s proteins to stimulate adenylate cyclase activity and increase production of the downstream effector cAMP (Nguyen et al., 2001). Alternatively, P2Y₁₂, P2Y₁₃ and P2Y₁₄ receptors are coupled to G_{i/o} proteins whose activation inhibits adenylate cyclase and decreases cAMP production (Abbracchio et al., 2006). Activation of P2YRs regulates numerous physiological and pathophysiological processes, including inflammation, cell growth, wound healing and thrombosis (Boeynaems et al., 2005; Burnstock and Verkhratsky, 2010; Gendaszewska-Darmach and Kucharska, 2011; Idzko et al., 2014). Within the CNS, P2Y receptors are expressed in neurons, astrocytes, oligodendrocytes and microglia with

physiological roles in neurotransmission, neurogenesis and glial cell communication (Burnstock et al., 1972; Guthrie et al., 1999; Fields and Burnstock, 2006; Mishra et al., 2006; Weisman et al., 2012a; Peterson et al., 2013). As the study of purinergic signaling in the CNS progresses, it has become increasingly clear that P2YRs play important pathophysiological roles where the activation of specific P2YR subtypes generates either neuroprotective or neurodegenerative responses making them novel targets for the treatment of CNS pathologies, including Alzheimer's disease (Davalos et al., 2005; Sperlagh and Illes, 2007; Burnstock, 2008; Kuboyama et al., 2011; Kim et al., 2012; Weisman et al., 2012a).

Previous investigations of AD brain samples demonstrated that the expression of the P2Y₁ receptor (P2Y₁R) is primarily localized to neurons in both AD and age-matched control brains. However, in the AD brain P2Y₁R expression also colocalized with neurofibrillary tangles and A β plaques, suggesting a possible role in AD pathology (Moore et al., 2000). While the role of neuronal P2Y₁R expression in AD brain remains unclear, *in vitro* studies of adult mouse neural stem cell (NSC) cultures have demonstrated that P2Y₁R activation by its endogenous agonist ADP induces proliferation of NSCs that is attenuated by the selective P2Y₁R antagonist MRS2179 (Mishra et al., 2006). Proliferation of NSCs is a crucial step during the process of neurogenesis in which new neurons are formed from self-renewing adult NSCs in the mammalian hippocampus (van Praag et al., 2002; Mu and Gage, 2011). Functional neurogenesis during adulthood has been demonstrated in both rodents and humans where it has been shown to contribute to hippocampus-dependent memory and cognition (Kuhn et al., 1996; Eriksson et al., 1998; Shors et al., 2001; Deng et al., 2010). Because degeneration of hippocampal neurons is a hallmark of AD, stimulating endogenous NSCs to increase neurogenesis has been suggested to be a potential regenerative therapy in AD to replace damaged neurons and improve cognition (Brinton and Wang, 2006; Mu and Gage, 2011; Fuster-Matanzo et al., 2013). Thus, the ability to increase NSC proliferation through P2Y₁R activation could be a novel therapeutic approach to promote regeneration of neurons in the hippocampus of AD patients. The cell-specific contributions of purinergic signaling have been clarified by recent work on the functional role of the P2Y₁R in glial cells, particularly astrocytes. In the APP^{swe}/PS1^{dE9} and APP+PS1 mouse models of AD, multiphoton fluorescence lifetime *in vivo* imaging (FLIM) was utilized to demonstrate that astrocytic networks in the AD mouse brain have significantly higher resting [Ca²⁺]_i levels than in wild type animals and exhibited increased propagation of intercellular calcium waves near A β plaques, which was suggested to contribute to A β -induced neuronal damage and synapse loss (Kuchibhotla et al., 2009; Delekate et al., 2014). Furthermore, expression of the P2Y₁R in the APP+PS1 mouse brain was shown to be primarily localized to reactive astrocytes near A β plaques and blockade of P2Y₁R signaling using the selective antagonist MRS2179 abolished the astrocytic hyperactivity and reduced [Ca²⁺]_i and intercellular calcium waves (Delekate et al., 2014), suggesting that P2Y₁R inhibition in astrocytes could be therapeutic in the treatment of AD.

Among P2Y receptors, the P2Y₂ receptor (P2Y₂R) is unique in that, in addition to canonical G_q-coupled activation of the PLC/IP₃/PKC pathway, it possesses several structural features allowing for interaction with other molecules to regulate cell migration, proliferation and growth factor release (Erb et al., 2001; Liu et al., 2004; Wang et al., 2005; Peterson et al., 2010; Ratchford et al., 2010). An Arg-Gly-Asp (RGD) motif in the first extracellular loop of

the P2Y₂R enables interaction with RGD-binding $\alpha_v\beta_3/5$ integrins and integrin-dependent activation of G_o and G₁₂ proteins that regulates the activities of the small GTPases Rho and Rac (Erb et al., 2001; Bagchi et al., 2005; Liao et al., 2007). In this way, activation of the P2Y₂R by its endogenous agonists ATP or UTP can stimulate Rho- and Rac-dependent cytoskeletal rearrangements and cell migration (Bagchi et al., 2005; Wang et al., 2005). Additionally, a binding site in the intracellular C-terminus allows P2Y₂R interaction with the actin-binding protein filamin A that also regulates P2Y₂R-mediated cell migration (Yu et al., 2008). Also within the C-terminus of the P2Y₂R, two Src-homology-3 (SH3) binding sites directly interact with and activate the tyrosine kinase Src, enabling P2Y₂R-mediated transactivation of growth factor receptors, including the EGFR (Liu et al., 2004). Lastly, the P2Y₂R has been shown to activate the α -secretases, ADAM10 and ADAM17, which promotes the release of membrane-bound receptor ligands, including growth factors (Ratchford et al., 2010; El-Sayed et al., 2014), and the cleavage of APP to form non-amyloidogenic sAPP α peptide (Camden et al., 2005; Kong et al., 2009).

Within the CNS, it appears that P2Y₂R activation is most relevant in regulating neuroprotective responses during neuroinflammation, as seen in AD. *In vitro*, P2Y₂R expression in rat primary cortical neurons is upregulated in response to IL-1 β (Kong et al., 2009), a well-described inflammatory cytokine whose levels are elevated in the AD brain (Shafteel et al., 2008), whereupon activation of the P2Y₂R by UTP stimulates neurite extension and non-amyloidogenic APP processing (Camden et al., 2005; Pooler et al., 2005; Kong et al., 2009; Peterson et al., 2013). In mouse primary microglial cells, P2Y₂R activation by UTP induces both the uptake and degradation of A β ₁₋₄₂ (Kim et al., 2012). These findings suggest multiple mechanisms for P2Y₂R-mediated neuroprotection, making it an attractive novel target for the treatment of AD. Consistent with these *in vitro* observations, global knockdown of P2Y₂R expression in the TgCRND8 mouse model of AD (*i.e.*, TgCRND8 $\times$ P2Y₂R^{+/-} mice) was shown to significantly increase AD-like pathology in the brain, including elevated A β ₁₋₄₂ levels, A β plaque deposition, leukocyte infiltration and neurological deficits leading to premature death at ~10 weeks of age (Ajit et al., 2014). These observations likely reflect the loss of P2Y₂R-mediated neuroprotective responses in both neurons and microglia investigated *in vitro*, as described above. Furthermore, P2Y₂R expression, but not P2Y₄ or P2Y₆ receptor expression, is selectively decreased in the parietal cortex of AD patients, as compared to age-matched non-AD controls, which correlates with synapse degeneration (Lai et al., 2008), consistent with the hypothesis that loss of P2Y₂R-mediated responses contributes to disease pathology in AD.

Similar to the P2Y₂R, the P2Y₄ receptor (P2Y₄R) has been shown to play a role in the uptake of A β ₁₋₄₂ by rat microglial cells through a mechanism dependent on autocrine ATP signaling (Li et al., 2013). Application of A β ₁₋₄₂ to primary mouse microglial cells has been shown to induce the release of ATP, which enhances cell migration and A β uptake that were inhibited by the addition of apyrase or P2Y₂R knockout (Kim et al., 2012). Autocrine ATP-induced A β uptake by microglia also was shown to be reduced following knockdown of the P2Y₄R in rats (Li et al., 2013), suggesting the presence of redundant regulators of ATP-induced A β uptake (*i.e.*, P2Y₂R and P2Y₄R), which should be exploited therapeutically to increase the uptake and degradation of A β ₁₋₄₂ in AD.

In addition to their role in A β clearance, microglial cells are the primary cells responsible for phagocytosis and clearance of dead neurons and debris in the AD brain that are necessary to maintain synapses and reduce neuroinflammation (Noda and Suzumura, 2012). The microglial P2Y₆ receptor (P2Y₆R), whose natural ligand is UDP, has been shown to be a primary regulator of the phagocytosis of damaged neurons in a kainic acid (KA)-induced model of neuronal cell death (Koizumi et al., 2007). Intraperitoneal application of KA, which has been shown to induce excitatory cell death, led to increased neuronal death in the rat hippocampus as well as increased P2Y₆R expression in microglial cells surrounding dying neurons. Furthermore, direct injection of KA into the hippocampus increased extracellular uridine nucleotide levels and phagocytic activity of microglia, which were attenuated by the P2Y₆R antagonist MRS2578 (Koizumi et al., 2007). However, targeting the P2Y₆R in the treatment of AD may be complicated by the recent finding that activated microglia can phagocytose viable neurons, a process termed phagoptosis (Brown and Neher, 2014). Exposure of neuron-microglial cell cocultures to sub-neurotoxic levels of A β ₁₋₄₂ (10–250 nM) has been shown to result in significant neuronal death, presumably through phagoptosis (Neniskyte et al., 2011). Further studies of this phenomenon demonstrated that inhibition of the P2Y₆R using MRS2578 significantly reduced phagoptosis in A β ₁₋₄₂-treated neuron-microglial cell cocultures and that the subsequent addition of UDP was sufficient to restore microglial cell-mediated neuronal death (Neher et al., 2014). Whether P2Y₆R agonism or antagonism represents a viable therapeutic approach in AD remains to be explored.

Lastly, microglial P2Y₁₂ and neuronal P2Y₁₃ receptors have been shown to activate neuroprotective responses by inducing microglial migration/filopodial extension towards injurious stimuli and protecting neurons from ROS-induced neurotoxicity, respectively. Microglia have been shown to extend filopodia and migrate towards focal neuron damage and P2Y₁₂ receptor (P2Y₁₂R) deficiency or inhibition abrogates ADP-induced chemotaxis and process extension, suggesting that microglial P2Y₁₂R activation may modulate neurodegeneration in the AD brain (Haynes et al., 2006; Koizumi et al., 2013; Webster et al., 2013). Activation of the P2Y₁₃ receptor (P2Y₁₃R) in rat primary cerebellar neurons using the selective agonist 2-methylthio-ADP has been shown to attenuate ROS-induced neuronal death through activation of Nrf2 (NF-E2-related factor-2) and downstream antioxidant response elements, suggesting that neuronal P2Y₁₃Rs could be targeted to reduce ROS-induced neurotoxicity during neuroinflammation (Espada et al., 2010).

4. Conclusion

The studies presented in this review highlight the research that has been done investigating the therapeutic potential of targeting purinergic receptors to treat Alzheimer's disease and the findings are summarized in Figure 1. Previous studies have identified the A_{2A}R, P2X₄R and P2X₇R as novel therapeutic drug targets whose antagonism or inhibition can reduce neurodegeneration. Targeting the P2Y₂R also may have therapeutic value, particularly in the early stages of disease where neuroinflammatory responses may play a role in tissue repair, as P2Y₂R activation in both neurons and microglia has been shown to promote neuroprotective responses. The P2Y₁R also may be relevant to AD pharmacotherapies, since P2Y₁R activation in neural stem cells enhances neurogenesis, whereas P2Y₁R activation in

astrocytes may contribute to neurodegeneration. The P2Y₆R in microglial cells has been shown to regulate phagocytosis of neuronal debris that should reduce neuroinflammation in the AD brain, but the same pathway can promote phagocytosis of viable neurons (*i.e.*, phagoptosis) that could contribute to neurodegeneration and, therefore, further studies are needed to evaluate the therapeutic potential of several P2YRs. Of major importance will be the continued development of potent and highly-specific P1 and P2 receptor agonists and antagonists that can be utilized in studies with animal models of AD and ultimately in human clinical trials. Nonetheless, current research strongly supports the relevance of P1 and P2 receptors as important targets in the treatment of AD and other neurodegenerative diseases, and clinical interest in these receptors is apparent with the announcement of a Phase II clinical trial to investigate the therapeutic use of intravenous ATP infusion to improve cerebral metabolism and mental state in AD patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02279511): NCT02279511).

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Abbreviations

Aβ	amyloid beta
ADAM10/17	a disintegrin and metalloproteinase domain 10/17
AD	Alzheimer's disease
APP	amyloid precursor protein
APP^{swe}	mutant APP bearing the Swedish mutation
BBG	Brilliant Blue G
ICV	intracerebroventricular
IP₃	inositol 1, 4, 5-trisphosphate
NLRP3	nucleotide-binding domain and leucine-rich repeat containing family, pyrin domain, containing 3
P2XR	P2X receptors
P2YR	P2Y receptors
PLC	phospholipase C
PKC	protein kinase C
PS1	presenilin 1
PS1^{ΔE9}	mutant presenilin 1 bearing the deltaE9 mutation
sAPP_α	soluble amyloid precursor protein α

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Highlights

- Alzheimer's disease is a neurodegenerative disorder resulting in loss of cognition
- Neuroinflammation is a major component of Alzheimer's disease
- Purinergic receptors can regulate neurodegeneration and neuroinflammation
- Purinergic receptors are novel drug targets to treat Alzheimer's disease

Figure 1. Purinergic receptors as novel drug targets to treat Alzheimer's disease

Numerous studies have utilized selective agonists and antagonists for purinergic receptors *in vitro* and in rodent models of Alzheimer's disease to demonstrate their therapeutic potential to treat AD. Neuronal P1 receptors (A₁R and A_{2A}R) have primarily been targeted to promote non-amyloidogenic amyloid precursor protein (APP) processing and prevent amyloid β -induced neurotoxicity. P2X and P2Y receptors have been targeted in neurons, microglia and astrocytes to enhance numerous therapeutic responses, including reducing neuroinflammation and neurotoxicity, enhancing non-amyloidogenic APP processing, promoting A β uptake and degradation and stimulating neurogenesis. This figure summarizes only the findings presented within this review paper and is not intended to be comprehensive.