Neuropharmacology xxx (2015) 1–11

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Purinergic receptors as potential therapeutic targets in Alzheimer's disease

Lucas T. Woods [a, c], Deepa Ajit [a, c], Jean M. Camden [a, c], Laurie Erb [a, c], Gary A. Weisman [a, b, c, *]

[a] Department of Biochemistry, University of Missouri, Columbia, MO, USA
[b] Interdisciplinary Neuroscience Program, University of Missouri, Columbia, MO, USA
[c] Christopher S. Bond Life Sciences Center, University of Missouri, Columbia, MO, USA

ARTICLE INFO

Article history:
Received 13 August 2015
Received in revised form
22 October 2015
Accepted 23 October 2015
Available online xxx

Keywords:
Alzheimer's disease
Neuroinflammation
P2Y receptor
P2X receptor
P1 receptor

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.

Contents

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

* Corresponding author. Department of Biochemistry, 540E Life Sciences Center, 1201 Rollins Road, University of Missouri, Columbia, MO 65211-7310, USA.
E-mail address: weismang@missouri.edu (G.A. Weisman).

http://dx.doi.org/10.1016/j.neuropharm.2015.10.031
0028-3908/

Abbreviations

Aβ	amyloid beta
ADAM10/17	a disintegrin and metalloproteinase domain 10/17
AD	Alzheimer's disease
APP	amyloid precursor protein
APPswe	mutant APP bearing the Swedish mutation
BBG	Brilliant Blue G
ICV	intracerebroventricular
IP_3	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
PS1dE9	mutant presenilin 1 bearing the deltaE9 mutation
sAPPα	soluble amyloid precursor protein α

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 post-mortem, 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-$\beta_{1\text{-}42}$ peptide (Aβ) that results from the sequential processing of amyloid precursor protein (APP) by β- and γ-secretases resulting in a buildup of neurotoxic Aβ 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 Aβ 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, 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-1β, 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 Aβ (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 Aβ 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 Aβ 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: NCT02279511). The therapeutic

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

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, 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 to 412 amino acids with 4 subtypes having been identified: A_1, A_{2A}, A_{2B} and A_3 receptors (Piirainen et al., 2011). These receptors can further be classified according to their preferred G protein interaction, where A_1 and A_3 receptors primarily couple to G_i protein leading to inhibition of adenylate 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 adenylate 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 A_3 receptors represent therapeutic targets in the CNS (Rosi et al., 2003; Chen et al., 2006; Popoli and Pepponi, 2012; Little et al., 2015), A_1 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, 2014; Pinna, 2014). Interestingly, the most widely consumed drug in the world, caffeine (Fredholm et al., 1999), is an A_1 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: 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 A_1 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 A_1 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 A_1 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 A_1 receptors was increased in degenerating neurons and around Aβ 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 A_1 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 A_1 receptor (A_1R) using the selective agonist (*R*)-N^6-(1-methyl-2-phenylethyl)adenosine (R-PIA) can enhance soluble APPα (sAPPα) production through a PKC- and ERK1/2-dependent mechanism suggesting that activation of the A_1R is neuroprotective by promoting α-secretase-mediated non-amyloidogenic sAPPα production (Angulo et al., 2003). A_1R-mediated sAPPα production was further shown to be attenuated by the selective A_1R 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 Aβ-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 A_1R 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 (APPswe) 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 $Aβ_{1-42}$ in the hippocampus (Arendash et al., 2006). Although the exact mechanism of caffeine-mediated neuroprotection was unclear, *in vitro* release of $Aβ_{1-40}$ and $Aβ_{1-42}$ was decreased in a dose-dependent manner following caffeine addition to differentiated N2a neuronal cells, suggesting that antagonism of neuronal A_1Rs and/or $A_{2A}Rs$ and decreased amyloidogenic Aβ production is neuroprotective (Arendash et al., 2006). In the APPswe and APP + PS1 mouse models of AD, short-term caffeine treatment (<24 h) reduced plasma Aβ levels in both ~3 month-old mice (before Aβ plaque development in the brain) and 15–20 month-old mice (after Aβ plaque development) (Cao et al., 2009). Furthermore, long-term caffeine treatment (4 weeks) in ~18 month-old APPswe mice was shown to reduce Aβ plaque load in the brain and reverse cognitive declines (Cao et al., 2009). In the intracerebroventricular (ICV) Aβ injection mouse model, which demonstrates Aβ-induced cognitive impairment and neurotoxicity, both caffeine and the selective $A_{2A}R$ antagonist SCH58261 were shown to prevent Aβ-induced cognitive impairments (Dall'Igna et al., 2007) and SCH58261 was further shown to

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

reduce synapse loss and hippocampal neuron toxicity following ICV Aβ administration in rats (Canas et al., 2009). Pharmacological A_{2A}R blockade also attenuated Aβ-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 A_1 and A_{2A} receptor antagonism in the brain as a therapeutic modality, it has been shown that A_1 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-Aβ antibodies, in the APPswe/PS1dE9 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 A_1 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 (P2XRs) are a family of ATP-gated cation channels ranging in size from 379 to 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.*, ATP^{4-}) is the primary agonist (Steinberg and Silverstein, 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-1β, a cytokine whose levels are elevated in the AD brain (Di Virgilio, 2007; Simi et al., 2007; Shaftel 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 Ca^{2+} signaling (Collo et al., 1997; Verderio and Matteoli, 2001; Sperlagh et al., 2002, 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, 2012; Chu 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 Aβ has been shown to increase P2X7R expression (McLarnon et al., 2006) and induce the release of proinflammatory cytokines, including TNFα, IL-6 and IL-1β (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-1β levels in the brain, as intrahippocampal Aβ injection causes a large accumulation of IL-1β in the hippocampi of wild type, but not $P2X7R^{-/-}$, mice (Sanz et al., 2009). The lack of Aβ-induced IL-1β accumulation in $P2X7R^{-/-}$ mouse hippocampus is likely due to the loss of microglial P2X7Rs, as *in vitro* studies have shown that Aβ increases ATP release, $[Ca^{2+}]_i$, and IL-1β 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 Aβ

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

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 Aβ 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 microglial 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 $A\beta_{1\text{-}42}$ was directly injected into the hippocampus, which led 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 $A\beta_{1\text{-}42}$ 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 Aβ injection significantly decreased Aβ-induced cognitive deficits. Furthermore, neuronal P2X7Rs appear to contribute to Aβ-induced neurodegeneration in mice, since *in vitro* studies using primary hippocampal neurons demonstrated that blockade of neuronal P2X7Rs by BBG attenuated Aβ-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 Aβ 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-3β), thus reducing the generation of Aβ and subsequent plaques, although decreased IL-1β 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 $A\beta_{1\text{-}42}$ peptide increases P2X4R expression and cell death (Varma et al., 2009). Furthermore, increasing P2X4R expression through lentiviral-based transfection led to increased $A\beta_{1\text{-}42}$-induced neuronal death, whereas decreasing P2X4R expression using P2X4R siRNA decreased Aβ-induced neuronal death (Varma et al., 2009). Neuronal death caused by Aβ was postulated to result from dysregulation of P2X4R-mediated Ca^{2+} influx whereby Aβ enhanced caspase 3-mediated cleavage of the P2X4R C-terminus thus increasing Ca^{2+} channel closure time and decreasing agonist-dependent receptor internalization from the cell membrane. As previous studies have already demonstrated that Aβ induces the release of the P2XR agonist ATP from microglia (Kim et al., 2007, 2012), it is suggested that increased Aβ 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 Aβ-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 ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11\text{-}14}$) 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 agonists to the $P2Y_2$ receptor (Lustig et al., 1992; Erb et al., 1995). $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$ and $P2Y_{11}$ receptors are coupled to the heterotrimeric G_q protein whose activation stimulates phospholipase C (PLC) and subsequent inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol generation leading to release of Ca^{2+} from intracellular stores and activation of protein kinase C (PKC), respectively (Abbracchio et al., 2006). The $P2Y_{11}$ receptor also couples to Gs proteins to stimulate adenylate cyclase activity and increase production of the downstream effector cAMP (Nguyen et al., 2001). Alternatively, $P2Y_{12}$, $P2Y_{13}$ and $P2Y_{14}$ 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 $P2Y_1$ receptor ($P2Y_1R$) is primarily localized to neurons in both AD and age-matched control brains. However, in the AD brain $P2Y_1R$ expression also colocalized with neurofibrillary tangles and Aβ plaques, suggesting a possible role in AD pathology (Moore et al., 2000). While the role of neuronal $P2Y_1R$ expression in AD brain remains unclear, *in vitro* studies of adult mouse neural stem cell (NSC) cultures have demonstrated that $P2Y_1R$ activation by its endogenous agonist ADP induces proliferation of NSCs that is attenuated by the selective $P2Y_1R$ 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-

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

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 $P2Y_1R$ 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 $P2Y_1R$ in glial cells, particularly astrocytes. In the APPswe/PS1dE9 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 $[Ca^{2+}]_i$ levels than in wild type animals and exhibited increased propagation of intercellular calcium waves near Aβ plaques, which was suggested to contribute to Aβ-induced neuronal damage and synapse loss (Kuchibhotla et al., 2009; Delekate et al., 2014). Furthermore, expression of the $P2Y_1R$ in the APP + PS1 mouse brain was shown to be primarily localized to reactive astrocytes near Aβ plaques and blockade of $P2Y_1R$ signaling using the selective antagonist MRS2179 abolished the astrocytic hyperactivity and reduced $[Ca^{2+}]_i$ and intercellular calcium waves (Delekate et al., 2014), suggesting that $P2Y_1R$ inhibition in astrocytes could be therapeutic in the treatment of AD.

Among P2Y receptors, the $P2Y_2$ receptor ($P2Y_2R$) is unique in that, in addition to canonical G_q-coupled activation of the PLC/IP_3/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 $P2Y_2R$ enables interaction with RGD-binding $\alpha_V\beta_{3/5}$ integrins and integrin-dependent activation of G_o and G_{12} 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 $P2Y_2R$ 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 $P2Y_2R$ interaction with the actin-binding protein filamin A that also regulates $P2Y_2R$-mediated cell migration (Yu et al., 2008). Also within the C-terminus of the $P2Y_2R$, two Src-homology-3 (SH3) binding sites directly interact with and activate the tyrosine kinase Src, enabling $P2Y_2R$-mediated transactivation of growth factor receptors, including the EGFR (Liu et al., 2004). Lastly, the $P2Y_2R$ 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 sAPPα peptide (Camden et al., 2005; Kong et al., 2009).

Within the CNS, it appears that $P2Y_2R$ activation is most relevant in regulating neuroprotective responses during neuroinflammation, as seen in AD. *In vitro*, $P2Y_2R$ expression in rat primary cortical neurons is upregulated in response to IL-1β (Kong et al., 2009), a well-described inflammatory cytokine whose levels are elevated in the AD brain (Shaftel et al., 2008), whereupon activation of the $P2Y_2R$ 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, $P2Y_2R$ activation by UTP induces both the uptake and degradation of $A\beta_{1\text{-}42}$ (Kim et al., 2012). These findings suggest multiple mechanisms for $P2Y_2R$-mediated neuroprotection, making it an attractive novel target for the treatment of AD. Consistent with these *in vitro* observations, global knockdown of $P2Y_2R$ expression in the TgCRND8 mouse model of AD (*i.e.*, TgCRND8 × $P2Y_2R^{+/-}$ mice) was shown to significantly increase AD-like pathology in the brain, including elevated $A\beta_{1\text{-}42}$ levels, Aβ 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 $P2Y_2R$-mediated neuroprotective responses in both neurons and microglia investigated *in vitro*, as described above. Furthermore, $P2Y_2R$ expression, but not $P2Y_4$ or $P2Y_6$ 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 $P2Y_2R$-mediated responses contributes to disease pathology in AD.

Similar to the $P2Y_2R$, the $P2Y_4$ receptor ($P2Y_4R$) has been shown to play a role in the uptake of $A\beta_{1\text{-}42}$ by rat microglial cells through a mechanism dependent on autocrine ATP signaling (Li et al., 2013). Application of $A\beta_{1\text{-}42}$ to primary mouse microglial cells has been shown to induce the release of ATP, which enhances cell migration and Aβ uptake that were inhibited by the addition of apyrase or $P2Y_2R$ knockout (Kim et al., 2012). Autocrine ATP-induced Aβ uptake by microglia also was shown to be reduced following knockdown of the $P2Y_4R$ in rats (Li et al., 2013), suggesting the presence of redundant regulators of ATP-induced Aβ uptake (*i.e.*, $P2Y_2R$ and $P2Y_4R$), which should be exploited therapeutically to increase the uptake and degradation of $A\beta_{1\text{-}42}$ in AD.

In addition to their role in Aβ 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 $P2Y_6$ receptor ($P2Y_6R$), 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 $P2Y_6R$ 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 $P2Y_6R$ antagonist MRS2578 (Koizumi et al., 2007). However, targeting the $P2Y_6R$ 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 $A\beta_{1\text{-}42}$ (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 $P2Y_6R$ using MRS2578 significantly reduced phagoptosis in $A\beta_{1\text{-}42}$-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 $P2Y_6R$ agonism or antagonism represents a viable therapeutic approach in AD remains to be explored.

Lastly, microglial $P2Y_{12}$ and neuronal $P2Y_{13}$ 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 $P2Y_{12}$ receptor ($P2Y_{12}R$) deficiency or inhibition abrogates ADP-induced chemotaxis and process

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

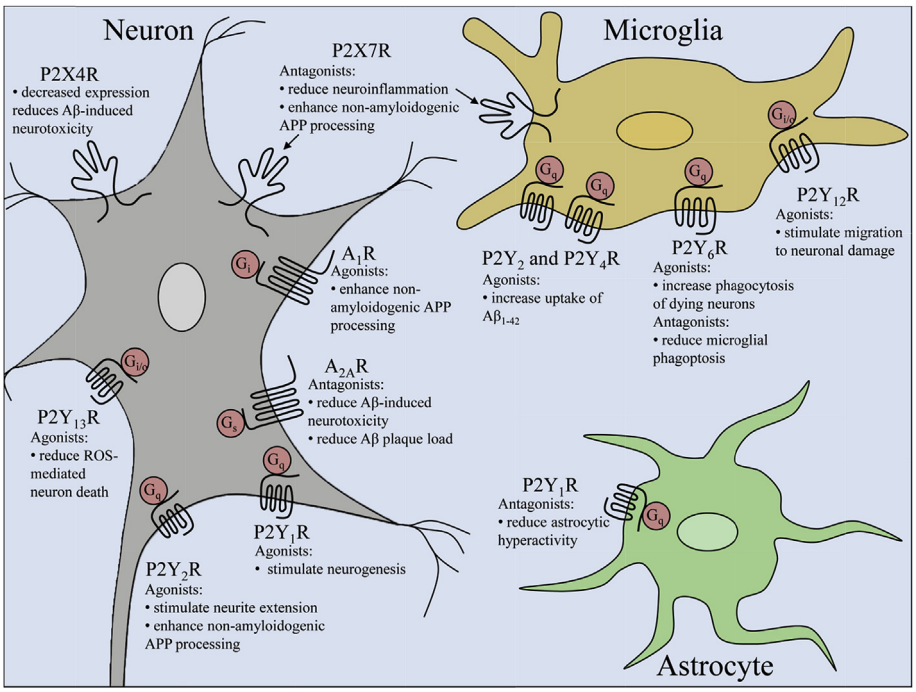

Fig. 1. Purinergic receptors as novel drug targets to treat Alzheimer's disease. Numerous studies have utilized selective agonists and antagonists for purinergic receptors *in vitro* and in rodent models of Alzheimer's disease to demonstrate their therapeutic potential to treat AD. Neuronal P1 receptors (A_1R 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 modulate numerous therapeutic responses, including reducing neuroinflammation and neurotoxicity, enhancing non-amyloidogenic APP processing, promoting Aβ uptake and degradation and stimulating neurogenesis. This figure summarizes only the findings presented within this review paper and is not intended to be comprehensive.

extension, suggesting that microglial $P2Y_{12}R$ activation may modulate neurodegeneration in the AD brain (Haynes et al., 2006; Koizumi et al., 2013; Webster et al., 2013). Activation of the $P2Y_{13}$ receptor ($P2Y_{13}R$) 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 $P2Y_{13}Rs$ 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 Fig. 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 $P2Y_2R$ also may have therapeutic value, particularly in the early stages of disease where neuroinflammatory responses may play a role in tissue repair, as $P2Y_2R$ activation in both neurons and microglia has been shown to promote neuroprotective responses. The $P2Y_1R$ also may be relevant to AD pharmacotherapies, since $P2Y_1R$ activation in neural stem cells enhances neurogenesis, whereas $P2Y_1R$ activation in astrocytes may contribute to neurodegeneration. The $P2Y_6R$ 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: NCT02279511).

Acknowledgments

This work was supported by NIH grant DE023342, BrightFocus Foundation grant A2013171S and a grant from the Spinal Cord Injuries Research Program of the University of Missouri.

References

Abbracchio, M.P., Burnstock, G., Boeynaems, J.M., Barnard, E.A., Boyer, J.L., Kennedy, C., Knight, G.E., Fumagalli, M., Gachet, C., Jacobson, K.A., Weisman, G.A., 2006. International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. Pharmacol. Rev. 58, 281–341.

Abbracchio, M.P., Ceruti, S., 2007. P1 receptors and cytokine secretion. Purinergic Signal 3, 13–25.

Agteresch, H.J., Dagnelie, P.C., van der Gaast, A., Stijnen, T., Wilson, J.H., 2000. Randomized clinical trial of adenosine 5′-triphosphate in patients with advanced non-small-cell lung cancer. J. Natl. Cancer Inst. 92, 321–328.

Aisen, P.S., Davis, K.L., Berg, J.D., Schafer, K., Campbell, K., Thomas, R.G., Weiner, M.F., Farlow, M.R., Sano, M., Grundman, M., Thal, L.J., 2000. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's disease cooperative study. Neurology 54, 588–593.

Aisen, P.S., Schafer, K.A., Grundman, M., Pfeiffer, E., Sano, M., Davis, K.L., Farlow, M.R., Jin, S., Thomas, R.G., Thal, L.J., 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 289, 2819–2826.

Ajit, D., Woods, L.T., Camden, J.M., Thebeau, C.N., El-Sayed, F.G., Greeson, G.W., Erb, L., Petris, M.J., Miller, D.C., Sun, G.Y., Weisman, G.A., 2014. Loss of $P2Y_2$

nucleotide receptors enhances early pathology in the TgCRND8 mouse model of Alzheimer's disease. Mol. Neurobiol. 49, 1031–1042.
Albasanz, J.L., Perez, S., Barrachina, M., Ferrer, I., Martin, M., 2008. Up-regulation of adenosine receptors in the frontal cortex in Alzheimer's disease. Brain Pathol. 18, 211–219.
Angulo, E., Casado, V., Mallol, J., Canela, E.I., Vinals, F., Ferrer, I., Lluis, C., Franco, R., 2003. A_1 adenosine receptors accumulate in neurodegenerative structures in Alzheimer disease and mediate both amyloid precursor protein processing and tau phosphorylation and translocation. Brain Pathol. 13, 440–451.
Apolloni, S., Montilli, C., Finocchi, P., Amadio, S., 2009. Membrane compartments and purinergic signalling: P2X receptors in neurodegenerative and neuroinflammatory events. FEBS J. 276, 354–364.
Arendash, G.W., Schleif, W., Rezai-Zadeh, K., Jackson, E.K., Zacharia, L.C., Cracchiolo, J.R., Shippy, D., Tan, J., 2006. Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain β-amyloid production. Neuroscience 142, 941–952.
Arulkumaran, N., Unwin, R.J., Tam, F.W., 2011. A potential therapeutic role for P2X7 receptor (P2X7R) antagonists in the treatment of inflammatory diseases. Expert Opin. Investig. Drugs 20, 897–915.
Ascherio, A., Zhang, S.M., Hernan, M.A., Kawachi, I., Colditz, G.A., Speizer, F.E., Willett, W.C., 2001. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann. Neurol. 50, 56–63.
Bagchi, S., Liao, Z., Gonzalez, F.A., Chorna, N.E., Seye, C.I., Weisman, G.A., Erb, L., 2005. The $P2Y_2$ nucleotide receptor interacts with α_v integrins to activate G_o and induce cell migration. J. Biol. Chem. 280, 39050–39057.
Beijer, S., Hupperets, P.S., van den Borne, B.E., Wijckmans, N.E., Spreeuwenberg, C., van den Brandt, P.A., Dagnelie, P.C., 2010. Randomized clinical trial on the effects of adenosine 5′-triphosphate infusions on quality of life, functional status, and fatigue in preterminal cancer patients. J. Pain Symptom Manag. 40, 520–530.
Boeynaems, J.M., van Giezen, H., Savi, P., Herbert, J.M., 2005. P2Y receptor antagonists in thrombosis. Curr. Opin. Investig. Drugs 6, 275–282.
Bours, M.J., Dagnelie, P.C., Giuliani, A.L., Wesselius, A., Di Virgilio, F., 2011. P2 receptors and extracellular ATP: a novel homeostatic pathway in inflammation. Front. Biosci. (Schol. Ed.) 3, 1443–1456.
Braak, H., Braak, E., 1996. Evolution of the neuropathology of Alzheimer's disease. Acta Neurol. Scand. Suppl. 165, 3–12.
Brinton, R.D., Wang, J.M., 2006. Therapeutic potential of neurogenesis for prevention and recovery from Alzheimer's disease: allopregnanolone as a proof of concept neurogenic agent. Curr. Alzheimer Res. 3, 185–190.
Brown, G.C., Neher, J.J., 2014. Microglial phagocytosis of live neurons. Nat. Rev. Neurosci. 15, 209–216.
Burnstock, G., 2006. Purinergic signalling. Br. J. Pharmacol. 147 (Suppl. 1), S172–S181.
Burnstock, G., 2008. Purinergic signalling and disorders of the central nervous system. Nat. Rev. Drug Discov. 7, 575–590.
Burnstock, G., 2010. Control of vascular tone by purines and pyrimidines. Br. J. Pharmacol. 161, 527–529.
Burnstock, G., 2015. An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration. Neuropharmacology. http://dx.doi.org/10.1016/j.neuropharm.2015.05.031 [Epub ahead of print].
Burnstock, G., Dumsday, B., Smythe, A., 1972. Atropine resistant excitation of the urinary bladder: the possibility of transmission via nerves releasing a purine nucleotide. Br. J. Pharmacol. 44, 451–461.
Burnstock, G., Krugel, U., Abbracchio, M.P., Illes, P., 2011. Purinergic signalling: from normal behaviour to pathological brain function. Prog. Neurobiol. 95, 229–274.
Burnstock, G., Verkhratsky, A., 2010. Long-term (trophic) purinergic signalling: purinoceptors control cell proliferation, differentiation and death. Cell Death Dis. 1, e9.
Butterfield, D.A., Boyd-Kimball, D., 2004. Amyloid β-peptide$_{1-42}$ contributes to the oxidative stress and neurodegeneration found in Alzheimer disease brain. Brain Pathol. 14, 426–432.
Camden, J.M., Schrader, A.M., Camden, R.E., Gonzalez, F.A., Erb, L., Seye, C.I., Weisman, G.A., 2005. $P2Y_2$ nucleotide receptors enhance α-secretase-dependent amyloid precursor protein processing. J. Biol. Chem. 280, 18696–18702.
Campion, D., Dumanchin, C., Hannequin, D., Dubois, B., Belliard, S., Puel, M., Thomas-Anterion, C., Michon, A., Martin, C., Charbonnier, F., Raux, G., Camuzat, A., Penet, C., Mesnage, V., Martinez, M., Clerget-Darpoux, F., Brice, A., Frebourg, T., 1999. Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum. Am. J. Hum. Genet. 65, 664–670.
Canas, P.M., Porciuncula, L.O., Cunha, G.M., Silva, C.G., Machado, N.J., Oliveira, J.M., Oliveira, C.R., Cunha, R.A., 2009. Adenosine A_{2A} receptor blockade prevents synaptotoxicity and memory dysfunction caused by β-amyloid peptides via p38 mitogen-activated protein kinase pathway. J. Neurosci. 29, 14741–14751.
Cao, C., Cirrito, J.R., Lin, X., Wang, L., Verges, D.K., Dickson, A., Mamcarz, M., Zhang, C., Mori, T., Arendash, G.W., Holtzman, D.M., Potter, H., 2009. Caffeine suppresses amyloid-β levels in plasma and brain of Alzheimer's disease transgenic mice. J. Alzheimers Dis. 17, 681–697.
Carman, A.J., Mills, J.H., Krenz, A., Kim, D.G., Bynoe, M.S., 2011. Adenosine receptor signaling modulates permeability of the blood-brain barrier. J. Neurosci. 31, 13272–13280.
Cauwels, A., Rogge, E., Vandendriessche, B., Shiva, S., Brouckaert, P., 2014. Extracellular ATP drives systemic inflammation, tissue damage and mortality. Cell Death Dis. 5, e1102.
Chakfe, Y., Seguin, R., Antel, J.P., Morissette, C., Malo, D., Henderson, D., Seguela, P., 2002. ADP and AMP induce interleukin-1β release from microglial cells through activation of ATP-primed P2X7 receptor channels. J. Neurosci. 22, 3061–3069.
Chen, G.J., Harvey, B.K., Shen, H., Chou, J., Victor, A., Wang, Y., 2006. Activation of adenosine A_3 receptors reduces ischemic brain injury in rodents. J. Neurosci. Res. 84, 1848–1855.
Chen, L., Brosnan, C.F., 2006. Exacerbation of experimental autoimmune encephalomyelitis in $P2X7R^{-/-}$ mice: evidence for loss of apoptotic activity in lymphocytes. J. Immunol. 176, 3115–3126.
Chen, X., Hu, J., Jiang, L., Xu, S., Zheng, B., Wang, C., Zhang, J., Wei, X., Chang, L., Wang, Q., 2014. Brilliant Blue G improves cognition in an animal model of Alzheimer's disease and inhibits amyloid-β-induced loss of filopodia and dendrite spines in hippocampal neurons. Neuroscience 279, 94–101.
Chizh, B.A., Illes, P., 2001. P2X receptors and nociception. Pharmacol. Rev. 53, 553–568.
Chrovian, C.C., Rech, J.C., Bhattacharya, A., Letavic, M.A., 2014. P2X7 antagonists as potential therapeutic agents for the treatment of CNS disorders. Prog. Med. Chem. 53, 65–100.
Chu, K., Yin, B., Wang, J., Peng, G., Liang, H., Xu, Z., Du, Y., Fang, M., Xia, Q., Luo, B., 2012. Inhibition of P2X7 receptor ameliorates transient global cerebral ischemia/reperfusion injury via modulating inflammatory responses in the rat hippocampus. J. Neuroinflamm. 9, 69.
Cole, G.M., Frautschy, S.A., 2010. Mechanisms of action of non-steroidal anti-inflammatory drugs for the prevention of Alzheimer's disease. CNS Neurol. Disord. Drug Targets 9, 140–148.
Collo, G., Neidhart, S., Kawashima, E., Kosco-Vilbois, M., North, R.A., Buell, G., 1997. Tissue distribution of the P2X7 receptor. Neuropharmacology 36, 1277–1283.
Combs, C.K., Karlo, J.C., Kao, S.C., Landreth, G.E., 2001. β-Amyloid stimulation of microglia and monocytes results in TNFα-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. J. Neurosci. 21, 1179–1188.
Csoka, B., Nemeth, Z.H., Toro, G., Idzko, M., Zech, A., Koscso, B., Spolarics, Z., Antonioli, L., Cseri, K., Erdelyi, K., Pacher, P., Hasko, G., 2015. Extracellular ATP protects against sepsis through macrophage P2X7 purinergic receptors by enhancing intracellular bacterial killing. FASEB J. 29, 3626–3637.
Cummings, J.L., 2004. Alzheimer's disease. New Engl. J. Med. 351, 56–67.
D'Andrea, M.R., Nagele, R.G., Wang, H.Y., Peterson, P.A., Lee, D.H., 2001. Evidence that neurones accumulating amyloid can undergo lysis to form amyloid plaques in Alzheimer's disease. Histopathology 38, 120–134.
Dall'Igna, O.P., Fett, P., Gomes, M.W., Souza, D.O., Cunha, R.A., Lara, D.R., 2007. Caffeine and adenosine A_{2A} receptor antagonists prevent β-amyloid$_{25-35}$-induced cognitive deficits in mice. Exp. Neurol. 203, 241–245.
Dall'Igna, O.P., Porciuncula, L.O., Souza, D.O., Cunha, R.A., Lara, D.R., 2003. Neuroprotection by caffeine and adenosine A_{2A} receptor blockade of β-amyloid neurotoxicity. Br. J. Pharmacol. 138, 1207–1209.
Davalos, D., Grutzendler, J., Yang, G., Kim, J.V., Zuo, Y., Jung, S., Littman, D.R., Dustin, M.L., Gan, W.B., 2005. ATP mediates rapid microglial response to local brain injury in vivo. Nat. Neurosci. 8, 752–758.
Delekate, A., Fuchtemeier, M., Schumacher, T., Ulbrich, C., Foddis, M., Petzold, G.C., 2014. Metabotropic P2Y1 receptor signalling mediates astrocytic hyperactivity in vivo in an Alzheimer's disease mouse model. Nat. Commun. 5, 5422.
Deng, W., Aimone, J.B., Gage, F.H., 2010. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat. Rev. Neurosci. 11, 339–350.
Di Virgilio, F., 1998. ATP as a death factor. Biofactors 8, 301–303.
Di Virgilio, F., 2007. Liaisons dangereuses: P2X7 and the inflammasome. Trends Pharmacol. Sci. 28, 465–472.
Diaz-Cabiale, Z., Hurd, Y., Guidolin, D., Finnman, U.B., Zoli, M., Agnati, L.F., Vanderhaeghen, J.J., Fuxe, K., Ferre, S., 2001. Adenosine A_{2A} agonist CGS 21680 decreases the affinity of dopamine D2 receptors for dopamine in human striatum. Neuroreport 12, 1831–1834.
Diaz-Hernandez, J.I., Gomez-Villafuertes, R., Leon-Otegui, M., Hontecillas-Prieto, L., Del Puerto, A., Trejo, J.L., Lucas, J.J., Garrido, J.J., Gualix, J., Miras-Portugal, M.T., Diaz-Hernandez, M., 2012. *In vivo* P2X7 inhibition reduces amyloid plaques in Alzheimer's disease through GSK3β and secretases. Neurobiol. Aging 33, 1816–1828.
Diaz-Hernandez, M., Diez-Zaera, M., Sanchez-Nogueiro, J., Gomez-Villafuertes, R., Canals, J.M., Alberch, J., Miras-Portugal, M.T., Lucas, J.J., 2009. Altered P2X7-receptor level and function in mouse models of Huntington's disease and therapeutic efficacy of antagonist administration. FASEB J. 23, 1893–1906.
El-Sayed, F.G., Camden, J.M., Woods, L.T., Khalafalla, M.G., Petris, M.J., Erb, L., Weisman, G.A., 2014. $P2Y_2$ nucleotide receptor activation enhances the aggregation and self-organization of dispersed salivary epithelial cells. Am. J. Physiol. Cell Physiol. 307, C83–C96.
Erb, L., Garrad, R., Wang, Y., Quinn, T., Turner, J.T., Weisman, G.A., 1995. Site-directed mutagenesis of P_{2U} purinoceptors. Positively charged amino acids in transmembrane helices 6 and 7 affect agonist potency and specificity. J. Biol. Chem. 270, 4185–4188.
Erb, L., Liu, J., Ockerhausen, J., Kong, Q., Garrad, R.C., Griffin, K., Neal, C., Krugh, B., Santiago-Perez, L.I., Gonzalez, F.A., Gresham, H.D., Turner, J.T., Weisman, G.A., 2001. An RGD sequence in the $P2Y_2$ receptor interacts with $\alpha_v\beta_3$ integrins and is required for G_o-mediated signal transduction. J. Cell Biol. 153, 491–501.
Erb, L., Lustig, K.D., Ahmed, A.H., Gonzalez, F.A., Weisman, G.A., 1990. Covalent incorporation of 3′-O-(4-benzoyl)benzoyl-ATP into a P2 purinoceptor in transformed mouse fibroblasts. J. Biol. Chem. 265, 7424–7431.
Eriksson, P.S., Perfilieva, E., Bjork-Eriksson, T., Alborn, A.M., Nordborg, C.,

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

Peterson, D.A., Gage, F.H., 1998. Neurogenesis in the adult human hippocampus. Nat. Med. 4, 1313–1317.
Eskelinen, M.H., Kivipelto, M., 2010. Caffeine as a protective factor in dementia and Alzheimer's disease. J. Alzheimers Dis. 20 (Suppl. 1), S167–S174.
Espada, S., Ortega, F., Molina-Jijon, E., Rojo, A.I., Perez-Sen, R., Pedraza-Chaverri, J., Miras-Portugal, M.T., Cuadrado, A., 2010. The purinergic $P2Y_{13}$ receptor activates the Nrf2/HO-1 axis and protects against oxidative stress-induced neuronal death. Free Radic. Biol. Med. 49, 416–426.
Fields, R.D., Burnstock, G., 2006. Purinergic signalling in neuron-glia interactions. Nat. Rev. Neurosci. 7, 423–436.
Flores, R.V., Hernandez-Perez, M.G., Aquino, E., Garrad, R.C., Weisman, G.A., Gonzalez, F.A., 2005. Agonist-induced phosphorylation and desensitization of the $P2Y_2$ nucleotide receptor. Mol. Cell Biochem. 280, 35–45.
Ford, A.P., 2012. In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization. Purinergic Signal 8, 3–26.
Frautschy, S.A., Yang, F., Irrizarry, M., Hyman, B., Saido, T.C., Hsiao, K., Cole, G.M., 1998. Microglial response to amyloid plaques in APPsw transgenic mice. Am. J. Pathol. 152, 307–317.
Fredholm, B.B., I. J., A.P., Jacobson, K.A., Klotz, K.N., Linden, J., 2001. International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. Pharmacol. Rev. 53, 527–552.
Fredholm, B.B., Battig, K., Holmen, J., Nehlig, A., Zvartau, E.E., 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol. Rev. 51, 83–133.
Fuster-Matanzo, A., Llorens-Martin, M., Hernandez, F., Avila, J., 2013. Role of neuroinflammation in adult neurogenesis and Alzheimer disease: therapeutic approaches. Mediat. Inflamm. 2013, 260925. Epub 2013 Apr 3.
Gandelman, M., Levy, M., Cassina, P., Barbeito, L., Beckman, J.S., 2013. P2X7 receptor-induced death of motor neurons by a peroxynitrite/FAS-dependent pathway. J. Neurochem. 126, 382–388.
Gendaszewska-Darmach, E., Kucharska, M., 2011. Nucleotide receptors as targets in the pharmacological enhancement of dermal wound healing. Purinergic Signal 7, 193–206.
Genin, E., Hannequin, D., Wallon, D., Sleegers, K., Hiltunen, M., Combarros, O., Bullido, M.J., Engelborghs, S., De Deyn, P., Berr, C., Pasquier, F., Dubois, B., Tognoni, G., Fievet, N., Brouwers, N., Bettens, K., Arosio, B., Coto, E., Del Zompo, M., Mateo, I., Epelbaum, J., Frank-Garcia, A., Helisalmi, S., Porcellini, E., Pilotto, A., Forti, P., Ferri, R., Scarpini, E., Siciliano, G., Solfrizzi, V., Sorbi, S., Spalletta, G., Valdivieso, F., Vepsalainen, S., Alvarez, V., Bosco, P., Mancuso, M., Panza, F., Nacmias, B., Bossu, P., Hanon, O., Piccardi, P., Annoni, G., Seripa, D., Galimberti, D., Licastro, F., Soininen, H., Dartigues, J.F., Kamboh, M.I., Van Broeckhoven, C., Lambert, J.C., Amouyel, P., Campion, D., 2011. APOE and Alzheimer disease: a major gene with semi-dominant inheritance. Mol. Psychiatry 16, 903–907.
Gilman, S., Koller, M., Black, R.S., Jenkins, L., Griffith, S.G., Fox, N.C., Eisner, L., Kirby, L., Rovira, M.B., Forette, F., Orgogozo, J.M., 2005. Clinical effects of Aβ immunization (AN1792) in patients with AD in an interrupted trial. Neurology 64, 1553–1562.
Green, R.C., Schneider, L.S., Amato, D.A., Beelen, A.P., Wilcock, G., Swabb, E.A., Zavitz, K.H., 2009. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: a randomized controlled trial. JAMA 302, 2557–2564.
Griffin, W.S., Stanley, L.C., Ling, C., White, L., MacLeod, V., Perrot, L.J., White 3rd, C.L., Araoz, C., 1989. Brain interleukin 1 and S-100 immunoreactivity are elevated in down syndrome and Alzheimer disease. Proc. Natl. Acad. Sci. U. S. A. 86, 7611–7615.
Guthrie, P.B., Knappenberger, J., Segal, M., Bennett, M.V., Charles, A.C., Kater, S.B., 1999. ATP released from astrocytes mediates glial calcium waves. J. Neurosci. 19, 520–528.
Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356.
Hauser, R.A., Cantillon, M., Pourcher, E., Micheli, F., Mok, V., Onofrj, M., Huyck, S., Wolski, K., 2011. Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. Lancet Neurol. 10, 221–229.
Hauser, R.A., Olanow, C.W., Kieburtz, K.D., Pourcher, E., Docu-Axelerad, A., Lew, M., Kozyolkin, O., Neale, A., Resburg, C., Meya, U., Kenney, C., Bandak, S., 2014. Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: a phase 2b, double-blind, randomised trial. Lancet Neurol. 13, 767–776.
Haynes, S.E., Hollopeter, G., Yang, G., Kurpius, D., Dailey, M.E., Gan, W.B., Julius, D., 2006. The $P2Y_{12}$ receptor regulates microglial activation by extracellular nucleotides. Nat. Neurosci. 9, 1512–1519.
Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A., 2013. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology 80, 1778–1783.
Heppner, F.L., Ransohoff, R.M., Becher, B., 2015. Immune attack: the role of inflammation in Alzheimer disease. Nat. Rev. Neurosci. 16, 358–372.
Hide, I., Tanaka, M., Inoue, A., Nakajima, K., Kohsaka, S., Inoue, K., Nakata, Y., 2000. Extracellular ATP triggers tumor necrosis factor-α release from rat microglia. J. Neurochem. 75, 965–972.
Huang, Y., Mucke, L., 2012. Alzheimer mechanisms and therapeutic strategies. Cell 148, 1204–1222.
Hurtado, D.E., Molina-Porcel, L., Iba, M., Aboagye, A.K., Paul, S.M., Trojanowski, J.Q., Lee, V.M.Y., 2010. Aβ accelerates the spatiotemporal progression of tau pathology and augments tau amyloidosis in an Alzheimer mouse model. Am. J. Pathol. 177, 1977–1988.
Idzko, M., Ferrari, D., Eltzschig, H.K., 2014. Nucleotide signalling during inflammation. Nature 509, 310–317.
Illes, P., Verkhratsky, A., Burnstock, G., Franke, H., 2012. P2X receptors and their roles in astroglia in the central and peripheral nervous system. Neuroscientist 18, 422–438.
Jansen, K.L., Faull, R.L., Dragunow, M., Synek, B.L., 1990. Alzheimer's disease: changes in hippocampal N-methyl-D-aspartate, quisqualate, neurotensin, adenosine, benzodiazepine, serotonin and opioid receptors–an autoradiographic study. Neuroscience 39, 613–627.
Jarvis, M.F., Burgard, E.C., McGaraughty, S., Honore, P., Lynch, K., Brennan, T.J., Subieta, A., Van Biesen, T., Cartmell, J., Bianchi, B., Niforatos, W., Kage, K., Yu, H., Mikusa, J., Wismer, C.T., Zhu, C.Z., Chu, K., Lee, C.H., Stewart, A.O., Polakowski, J., Cox, B.F., Kowaluk, E., Williams, M., Sullivan, J., Faltynek, C., 2002. A-317491, a novel potent and selective non-nucleotide antagonist of P2X3 and P2X2/3 receptors, reduces chronic inflammatory and neuropathic pain in the rat. Proc. Natl. Acad. Sci. U. S. A. 99, 17179–17184.
Jiang, L.H., Mackenzie, A.B., North, R.A., Surprenant, A., 2000. Brilliant blue G selectively blocks ATP-gated rat P2X7 receptors. Mol. Pharmacol. 58, 82–88.
Kalaria, R.N., Sromek, S., Wilcox, B.J., Unnerstall, J.R., 1990. Hippocampal adenosine A1 receptors are decreased in Alzheimer's disease. Neurosci. Lett. 118, 257–260.
Kanjhan, R., Housley, G.D., Burton, L.D., Christie, D.L., Kippenberger, A., Thorne, P.R., Luo, L., Ryan, A.F., 1999. Distribution of the P2X2 receptor subunit of the ATP-gated ion channels in the rat central nervous system. J. Comp. Neurol. 407, 11–32.
Khakh, B.S., North, R.A., 2006. P2X receptors as cell-surface ATP sensors in health and disease. Nature 442, 527–532.
Kim, H.J., Ajit, D., Peterson, T.S., Wang, Y., Camden, J.M., Gibson Wood, W., Sun, G.Y., Erb, L., Petris, M., Weisman, G.A., 2012. Nucleotides released from $Aβ_{1-42}$-treated microglial cells increase cell migration and $Aβ_{1-42}$ uptake through $P2Y_2$ receptor activation. J. Neurochem. 121, 228–238.
Kim, S.Y., Moon, J.H., Lee, H.G., Kim, S.U., Lee, Y.B., 2007. ATP released from β-amyloid-stimulated microglia induces reactive oxygen species production in an autocrine fashion. Exp. Mol. Med. 39, 820–827.
Koizumi, S., Ohsawa, K., Inoue, K., Kohsaka, S., 2013. Purinergic receptors in microglia: functional modal shifts of microglia mediated by P2 and P1 receptors. Glia 61, 47–54.
Koizumi, S., Shigemoto-Mogami, Y., Nasu-Tada, K., Shinozaki, Y., Ohsawa, K., Tsuda, M., Joshi, B.V., Jacobson, K.A., Kohsaka, S., Inoue, K., 2007. UDP acting at $P2Y_6$ receptors is a mediator of microglial phagocytosis. Nature 446, 1091–1095.
Koles, L., Furst, S., Illes, P., 2007. Purine ionotropic (P2X) receptors. Curr. Pharm. Des. 2368–2384.
Kong, Q., Peterson, T.S., Baker, O., Stanley, E., Camden, J., Seye, C.I., Erb, L., Simonyi, A., Wood, W.G., Sun, G.Y., Weisman, G.A., 2009. Interleukin-1β enhances nucleotide-induced and α-secretase-dependent amyloid precursor protein processing in rat primary cortical neurons via up-regulation of the $P2Y_2$ receptor. J. Neurochem. 109, 1300–1310.
Kong, Q., Wang, M., Liao, Z., Camden, J.M., Yu, S., Simonyi, A., Sun, G.Y., Gonzalez, F.A., Erb, L., Seye, C.I., Weisman, G.A., 2005. P2X7 nucleotide receptors mediate caspase-8/9/3-dependent apoptosis in rat primary cortical neurons. Purinergic Signal 1, 337–347.
Kowall, N.W., Beal, M.F., Busciglio, J., Duffy, L.K., Yankner, B.A., 1991. An in vivo model for the neurodegenerative effects of β-amyloid and protection by substance P. Proc. Natl. Acad. Sci. U. S. A. 88, 7247–7251.
Kuboyama, K., Harada, H., Tozaki-Saitoh, H., Tsuda, M., Ushijima, K., Inoue, K., 2011. Astrocytic $P2Y_1$ receptor is involved in the regulation of cytokine/chemokine transcription and cerebral damage in a rat model of cerebral ischemia. J. Cereb. Blood Flow Metab. 31, 1930–1941.
Kuchibhotla, K.V., Lattarulo, C.R., Hyman, B.T., Bacskai, B.J., 2009. Synchronous hyperactivity and intercellular calcium waves in astrocytes in Alzheimer mice. Science 323, 1211–1215.
Kuhn, H.G., Dickinson-Anson, H., Gage, F.H., 1996. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J. Neurosci. 16, 2027–2033.
Lai, M.K., Tan, M.G., Kirvell, S., Hobbs, C., Lee, J., Esiri, M.M., Chen, C.P., Francis, P.T., 2008. Selective loss of $P2Y_2$ nucleotide receptor immunoreactivity is associated with Alzheimer's disease neuropathology. J. Neural Transm. 115, 1165–1172.
Lee, H.G., Won, S.M., Gwag, B.J., Lee, Y.B., 2011. Microglial P2X7 receptor expression is accompanied by neuronal damage in the cerebral cortex of the APPswe/PS1dE9 mouse model of Alzheimer's disease. Exp. Mol. Med. 43, 7–14.
Lemere, C.A., Lopera, F., Kosik, K.S., Lendon, C.L., Ossa, J., Saido, T.C., Yamaguchi, H., Ruiz, A., Martinez, A., Madrigal, L., Hincapie, L., Arango, J.C., Anthony, D.C., Koo, E.H., Goate, A.M., Selkoe, D.J., 1996. The E280A presenilin 1 Alzheimer mutation produces increased Aβ 42 deposition and severe cerebellar pathology. Nat. Med. 2, 1146–1150.
LeWitt, P.A., Guttman, M., Tetrud, J.W., Tuite, P.J., Mori, A., Chaikin, P., Sussman, N.M., 2008. Adenosine A_{2A} receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann. Neurol. 63, 295–302.
Li, H.Q., Chen, C., Dou, Y., Wu, H.J., Liu, Y.J., Lou, H.F., Zhang, J.M., Li, X.M., Wang, H., Duan, S., 2013. $P2Y_4$ receptor-mediated pinocytosis contributes to amyloid β-induced self-uptake by microglia. Mol. Cell Biol. 33, 4282–4293.
Liao, Z., Seye, C.I., Weisman, G.A., Erb, L., 2007. The $P2Y_2$ nucleotide receptor requires interaction with $α_v$ integrins to access and activate G_{12}. J. Cell Sci. 120,

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

1654–1662.
Lister, M.F., Sharkey, J., Sawatzky, D.A., Hodgkiss, J.P., Davidson, D.J., Rossi, A.G., Finlayson, K., 2007. The role of the purinergic P2X7 receptor in inflammation. J. Inflamm. (Lond.) 4, 5.
Little, J.W., Ford, A., Symons-Liguori, A.M., Chen, Z., Janes, K., Doyle, T., Xie, J., Luongo, L., Tosh, D.K., Maione, S., Bannister, K., Dickenson, A.H., Vanderah, T.W., Porreca, F., Jacobson, K.A., Salvemini, D., 2015. Endogenous adenosine A_3 receptor activation selectively alleviates persistent pain states. Brain 138, 28–35.
Liu, J., Liao, Z., Camden, J., Griffin, K.D., Garrad, R.C., Santiago-Perez, L.I., Gonzalez, F.A., Seye, C.I., Weisman, G.A., Erb, L., 2004. Src homology 3 binding sites in the $P2Y_2$ nucleotide receptor interact with Src and regulate activities of Src, proline-rich tyrosine kinase 2, and growth factor receptors. J. Biol. Chem. 279, 8212–8218.
Lucattelli, M., Cicko, S., Muller, T., Lommatzsch, M., De Cunto, G., Cardini, S., Sundas, W., Grimm, M., Zeiser, R., Durk, T., Zissel, G., Sorichter, S., Ferrari, D., Di Virgilio, F., Virchow, J.C., Lungarella, G., Idzko, M., 2011. P2X7 receptor signaling in the pathogenesis of smoke-induced lung inflammation and emphysema. Am. J. Respir. Cell Mol. Biol. 44, 423–429.
Lustig, K.D., Sportiello, M.G., Erb, L., Weisman, G.A., 1992. A nucleotide receptor in vascular endothelial cells is specifically activated by the fully ionized forms of ATP and UTP. Biochem. J. 284 (Pt 3), 733–739.
Maia, L., de Mendonca, A., 2002. Does caffeine intake protect from Alzheimer's disease? Eur. J. Neurol. Soc. 9, 377–382.
Malin, D.H., Crothers, M.K., Lake, J.R., Goyarzu, P., Plotner, R.E., Garcia, S.A., Spell, S.H., Tomsic, B.J., Giordano, T., Kowall, N.W., 2001. Hippocampal injections of amyloid β-peptide 1-40 impair subsequent one-trial/day reward learning. Neurobiol. Learn. Mem. 76, 125–137.
Matute, C., Torre, I., Perez-Cerda, F., Perez-Samartin, A., Alberdi, E., Etxebarria, E., Arranz, A.M., Ravid, R., Rodriguez-Antiguedad, A., Sanchez-Gomez, M., Domercq, M., 2007. P2X7 receptor blockade prevents ATP excitotoxicity in oligodendrocytes and ameliorates experimental autoimmune encephalomyelitis. J. Neurosci. 27, 9525–9533.
McGaraughty, S., Wismer, C.T., Zhu, C.Z., Mikusa, J., Honore, P., Chu, K.L., Lee, C.H., Faltynek, C.R., Jarvis, M.F., 2003. Effects of A-317491, a novel and selective P2X3/P2X2/3 receptor antagonist, on neuropathic, inflammatory and chemogenic nociception following intrathecal and intraplantar administration. Br. J. Pharmacol. 140, 1381–1388.
McLarnon, J.G., Ryu, J.K., Walker, D.G., Choi, H.B., 2006. Upregulated expression of purinergic P2X7 receptor in Alzheimer disease and amyloid-β peptide-treated microglia and in peptide-injected rat hippocampus. J. Neuropathol. Exp. Neurol. 65, 1090–1097.
Mishina, M., Ishiwata, K., Naganawa, M., Kimura, Y., Kitamura, S., Suzuki, M., Hashimoto, M., Ishibashi, K., Oda, K., Sakata, M., Hamamoto, M., Kobayashi, S., Katayama, Y., Ishii, K., 2011. Adenosine A_{2A} receptors measured with [C]TMSX PET in the striata of Parkinson's disease patients. PLoS One 6, e17338.
Mishra, S.K., Braun, N., Shukla, V., Fullgrabe, M., Schomerus, C., Korf, H.W., Gachet, C., Ikehara, Y., Sevigny, J., Robson, S.C., Zimmermann, H., 2006. Extracellular nucleotide signaling in adult neural stem cells: synergism with growth factor-mediated cellular proliferation. Development 133, 675–684.
Monif, M., Reid, C.A., Powell, K.L., Smart, M.L., Williams, D.A., 2009. The P2X7 receptor drives microglial activation and proliferation: a trophic role for P2X7R pore. J. Neurosci. 29, 3781–3791.
Moore, D., Iritani, S., Chambers, J., Emson, P., 2000. Immunohistochemical localization of the $P2Y_1$ purinergic receptor in Alzheimer's disease. Neuroreport 11, 3799–3803.
Morelli, M., Carta, A.R., Kachroo, A., Schwarzschild, M.A., 2010. Pathophysiological roles for purines: adenosine, caffeine and urate. Prog. Brain Res. 183, 183–208.
Mu, Y., Gage, F.H., 2011. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol. Neurodegener. 6, 85.
Nagele, R.G., D'Andrea, M.R., Lee, H., Venkataraman, V., Wang, H.Y., 2003. Astrocytes accumulate Aβ 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. Brain Res. 971, 197–209.
Neher, J.J., Neniskyte, U., Hornik, T., Brown, G.C., 2014. Inhibition of UDP/$P2Y_6$ purinergic signaling prevents phagocytosis of viable neurons by activated microglia *in vitro* and *in vivo*. Glia 62, 1463–1475.
Neniskyte, U., Neher, J.J., Brown, G.C., 2011. Neuronal death induced by nanomolar amyloid β is mediated by primary phagocytosis of neurons by microglia. J. Biol. Chem. 286, 39904–39913.
Nguyen, T.D., Meichle, S., Kim, U.S., Wong, T., Moody, M.W., 2001. $P2Y_{11}$, a purinergic receptor acting via cAMP, mediates secretion by pancreatic duct epithelial cells. Am. J. Physiol. Gastrointest. Liver Physiol. 280, G795–G804.
Noda, M., Suzumura, A., 2012. Sweepers in the CNS: microglial migration and phagocytosis in the Alzheimer disease pathogenesis. Int. J. Alzheimers Dis. 2012, 891087.
O'Brien, R.J., Wong, P.C., 2011. Amyloid precursor protein processing and Alzheimer's disease. Annu. Rev. Neurosci. 34, 185–204.
Obulesu, M., Venu, R., Somashekhar, R., 2011. Tau mediated neurodegeneration: an insight into Alzheimer's disease pathology. Neurochem. Res. 36, 1329–1335.
Parajuli, B., Sonobe, Y., Horiuchi, H., Takeuchi, H., Mizuno, T., Suzumura, A., 2013. Oligomeric amyloid β induces IL-1β processing via production of ROS: implication in Alzheimer's disease. Cell Death Dis. 4, e975.
Parvathenani, L.K., Tertyshnikova, S., Greco, C.R., Roberts, S.B., Robertson, B., Posmantur, R., 2003. P2X7 mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease. J. Biol. Chem. 278, 13309–13317.
Patel, N.S., Paris, D., Mathura, V., Quadros, A.N., Crawford, F.C., Mullan, M.J., 2005. Inflammatory cytokine levels correlate with amyloid load in transgenic mouse models of Alzheimer's disease. J. Neuroinflamm. 2, 9.
Pekny, M., Wilhelmsson, U., Pekna, M., 2014. The dual role of astrocyte activation and reactive gliosis. Neurosci. Lett. 565, 30–38.
Perregaux, D.G., McNiff, P., Laliberte, R., Conklyn, M., Gabel, C.A., 2000. ATP acts as an agonist to promote stimulus-induced secretion of IL-1β and IL-18 in human blood. J. Immunol. 165, 4615–4623.
Peterson, T.S., Camden, J.M., Wang, Y., Seye, C.I., Wood, W.G., Sun, G.Y., Erb, L., Petris, M.J., Weisman, G.A., 2010. $P2Y_2$ nucleotide receptor-mediated responses in brain cells. Mol. Neurobiol. 41, 356–366.
Peterson, T.S., Thebeau, C.N., Ajit, D., Camden, J.M., Woods, L.T., Wood, W.G., Petris, M.J., Sun, G.Y., Erb, L., Weisman, G.A., 2013. Up-regulation and activation of the $P2Y_2$ nucleotide receptor mediate neurite extension in IL-1β-treated mouse primary cortical neurons. J. Neurochem. 125, 885–896.
Piirainen, H., Ashok, Y., Nanekar, R.T., Jaakola, V.P., 2011. Structural features of adenosine receptors: from crystal to function. Biochim. Biophys. Acta 1808, 1233–1244.
Pinna, A., 2014. Adenosine A_{2A} receptor antagonists in Parkinson's disease: progress in clinical trials from the newly approved istradefylline to drugs in early development and those already discontinued. CNS Drugs 28, 455–474.
Pooler, A.M., Guez, D.H., Benedictus, R., Wurtman, R.J., 2005. Uridine enhances neurite outgrowth in nerve growth factor-differentiated PC12 [corrected]. Neuroscience 134, 207–214.
Popoli, P., Pepponi, R., 2012. Potential therapeutic relevance of adenosine A_{2B} and A_{2A} receptors in the central nervous system. CNS Neurol. Disord. Drug Targets 11, 664–674.
Popoli, P., Pintor, A., Domenici, M.R., Frank, C., Tebano, M.T., Pezzola, A., Scarchilli, L., Quarta, D., Reggio, R., Malchiodi-Albedi, F., Falchi, M., Massotti, M., 2002. Blockade of striatal adenosine A_{2A} receptor reduces, through a presynaptic mechanism, quinolinic acid-induced excitotoxicity: possible relevance to neuroprotective interventions in neurodegenerative diseases of the striatum. J. Neurosci. 22, 1967–1975.
Rahman, A., 2009. The role of adenosine in Alzheimer's disease. Curr. Neuropharmacol. 7, 207–216.
Ratchford, A.M., Baker, O.J., Camden, J.M., Rikka, S., Petris, M.J., Seye, C.I., Erb, L., Weisman, G.A., 2010. $P2Y_2$ nucleotide receptors mediate metalloprotease-dependent phosphorylation of epidermal growth factor receptor and ErbB3 in human salivary gland cells. J. Biol. Chem. 285, 7545–7555.
Rivera-Oliver, M., Diaz-Rios, M., 2014. Using caffeine and other adenosine receptor antagonists and agonists as therapeutic tools against neurodegenerative diseases: a review. Life Sci. 101, 1–9.
Rodrigues, R.J., Almeida, T., Richardson, P.J., Oliveira, C.R., Cunha, R.A., 2005. Dual presynaptic control by ATP of glutamate release via facilitatory P2X1, P2X2/3, and P2X3 and inhibitory $P2Y_1$, $P2Y_2$, and/or $P2Y_4$ receptors in the rat hippocampus. J. Neurosci. 25, 6286–6295.
Roger, S., Pelegrin, P., Surprenant, A., 2008. Facilitation of P2X7 receptor currents and membrane blebbing via constitutive and dynamic calmodulin binding. J. Neurosci. 28, 6393–6401.
Rosi, S., McGann, K., Hauss-Wegrzyniak, B., Wenk, G.L., 2003. The influence of brain inflammation upon neuronal adenosine A_{2B} receptors. J. Neurochem. 86, 220–227.
Rubio, M.E., Soto, F., 2001. Distinct localization of P2X receptors at excitatory postsynaptic specializations. J. Neurosci. 21, 641–653.
Ryu, J.K., McLarnon, J.G., 2008. Block of purinergic P2X7 receptor is neuroprotective in an animal model of Alzheimer's disease. Neuroreport 19, 1715–1719.
Salloway, S., Sperling, R., Gilman, S., Fox, N.C., Blennow, K., Raskind, M., Sabbagh, M., Honig, L.S., Doody, R., van Dyck, C.H., Mulnard, R., Barakos, J., Gregg, K.M., Liu, E., Lieberburg, I., Schenk, D., Black, R., Grundman, M., 2009. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. Neurology 73, 2061–2070.
Sanz, J.M., Chiozzi, P., Ferrari, D., Colaianna, M., Idzko, M., Falzoni, S., Fellin, R., Trabace, L., Di Virgilio, F., 2009. Activation of microglia by amyloid β requires P2X7 receptor expression. J. Immunol. 182, 4378–4385.
Scharf, S., Mander, A., Ugoni, A., Vajda, F., Christophidis, N., 1999. A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. Neurology 53, 197–201.
Schlachetzki, J.C., Hull, M., 2009. Microglial activation in Alzheimer's disease. Curr. Alzheimer Res. 6, 554–563.
Schor, N.F., 2011. What the halted phase III γ-secretase inhibitor trial may (or may not) be telling us. Ann. Neurol. 69, 237–239.
Schwarzschild, M.A., Agnati, L., Fuxe, K., Chen, J.F., Morelli, M., 2006. Targeting adenosine A_{2A} receptors in Parkinson's disease. Trends Neurosci. 29, 647–654.
Shaftel, S.S., Griffin, W.S., O'Banion, M.K., 2008. The role of interleukin-1 in neuroinflammation and Alzheimer disease: an evolving perspective. J. Neuroinflamm. 5, 7.
Shieh, C.H., Heinrich, A., Serchov, T., van Calker, D., Biber, K., 2014. P2X7-dependent, but differentially regulated release of IL-6, CCL2, and TNF-α in cultured mouse microglia. Glia 62, 592–607.
Shors, T.J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., Gould, E., 2001. Neurogenesis in the adult is involved in the formation of trace memories. Nature 410, 372–376.
Simi, A., Lerouet, D., Pinteaux, E., Brough, D., 2007. Mechanisms of regulation for interleukin-1β in neurodegenerative disease. Neuropharmacology 52, 1563–1569.

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031

Simpson, J.E., Ince, P.G., Lace, G., Forster, G., Shaw, P.J., Matthews, F., Savva, G., Brayne, C., Wharton, S.B., 2010. Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain. Neurobiol. Aging 31, 578–590.

Sperlagh, B., Illes, P., 2007. Purinergic modulation of microglial cell activation. Purinergic Signal 3, 117–127.

Sperlagh, B., Kofalvi, A., Deuchars, J., Atkinson, L., Milligan, C.J., Buckley, N.J., Vizi, E.S., 2002. Involvement of P2X7 receptors in the regulation of neurotransmitter release in the rat hippocampus. J. Neurochem. 81, 1196–1211.

Sperlagh, B., Vizi, E.S., Wirkner, K., Illes, P., 2006. P2X7 receptors in the nervous system. Prog. Neurobiol. 78, 327–346.

Stagg, J., Smyth, M.J., 2010. Extracellular adenosine triphosphate and adenosine in cancer. Oncogene 29, 5346–5358.

Steinberg, T.H., Silverstein, S.C., 1987. Extracellular ATP^{4-} promotes cation fluxes in the J774 mouse macrophage cell line. J. Biol. Chem. 262, 3118–3122.

Stone, T.W., Ceruti, S., Abbracchio, M.P., 2009. Adenosine receptors and neurological disease: neuroprotection and neurodegeneration. Handb. Exp. Pharmacol. 193, 535–587.

Suzuki, T., Hide, I., Ido, K., Kohsaka, S., Inoue, K., Nakata, Y., 2004. Production and release of neuroprotective tumor necrosis factor by P2X7 receptor-activated microglia. J. Neurosci. 24, 1–7.

Tanaka, J., Murate, M., Wang, C.Z., Seino, S., Iwanaga, T., 1996. Cellular distribution of the P2X4 ATP receptor mRNA in the brain and non-neuronal organs of rats. Arch. Histol. Cytol. 59, 485–490.

Trautmann, A., 2009. Extracellular ATP in the immune system: more than just a "danger signal". Sci. Signal 2, e6.

Tsuda, M., Shigemoto-Mogami, Y., Koizumi, S., Mizokoshi, A., Kohsaka, S., Salter, M.W., Inoue, K., 2003. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature 424, 778–783.

Tsuda, M., Tozaki-Saitoh, H., Inoue, K., 2009. Pain and purinergic signaling. Brain Res. Rev. 63, 222–232.

Ulas, J., Brunner, L.C., Nguyen, L., Cotman, C.W., 1993. Reduced density of adenosine A_1 receptors and preserved coupling of adenosine A_1 receptors to G proteins in Alzheimer hippocampus: a quantitative autoradiographic study. Neuroscience 52, 843–854.

Ulmann, L., Hatcher, J.P., Hughes, J.P., Chaumont, S., Green, P.J., Conquet, F., Buell, G.N., Reeve, A.J., Chessell, I.P., Rassendren, F., 2008. Up-regulation of P2X4 receptors in spinal microglia after peripheral nerve injury mediates BDNF release and neuropathic pain. J. Neurosci. 28, 11263–11268.

van Gelder, B.M., Buijsse, B., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., Kromhout, D., 2007. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE study. Eur. J. Clin. Nutr. 61, 226–232.

van Praag, H., Schinder, A.F., Christie, B.R., Toni, N., Palmer, T.D., Gage, F.H., 2002. Functional neurogenesis in the adult hippocampus. Nature 415, 1030–1034.

Varma, R., Chai, Y., Troncoso, J., Gu, J., Xing, H., Stojilkovic, S.S., Mattson, M.P., Haughey, N.J., 2009. Amyloid-β induces a caspase-mediated cleavage of P2X4 to promote purinotoxicity. Neuromol. Med. 11, 63–75.

Verderio, C., Matteoli, M., 2001. ATP mediates calcium signaling between astrocytes and microglial cells: modulation by IFN-γ. J. Immunol. 166, 6383–6391.

Verhoef, P.A., Estacion, M., Schilling, W., Dubyak, G.R., 2003. P2X7 receptor-dependent blebbing and the activation of Rho-effector kinases, caspases, and IL-1β release. J. Immunol. 170, 5728–5738.

Vial, C., Roberts, J.A., Evans, R.J., 2004. Molecular properties of ATP-gated P2X receptor ion channels. Trends Pharmacol. Sci. 25, 487–493.

Villalona-Calero, M.A., Otterson, G.A., Wientjes, M.G., Weber, F., Bekaii-Saab, T., Young, D., Murgo, A.J., Jensen, R., Yeh, T.K., Wei, Y., Zhang, Y., Eng, C., Grever, M., Au, J.L., 2008. Noncytotoxic suramin as a chemosensitizer in patients with advanced non-small-cell lung cancer: a phase II study. Ann. Oncol. 19, 1903–1909.

Villar-Menendez, I., Porta, S., Buira, S.P., Pereira-Veiga, T., Diaz-Sanchez, S., Albasanz, J.L., Ferrer, I., Martin, M., Barrachina, M., 2014. Increased striatal adenosine A_{2A} receptor levels is an early event in Parkinson's disease-related pathology and it is potentially regulated by miR-34b. Neurobiol. Dis. 69, 206–214.

Wang, M., Kong, Q., Gonzalez, F.A., Sun, G., Erb, L., Seye, C., Weisman, G.A., 2005. P2Y nucleotide receptor interaction with α integrin mediates astrocyte migration. J. Neurochem. 95, 630–640.

Watano, T., Calvert, J.A., Vial, C., Forsythe, I.D., Evans, R.J., 2004. P2X receptor subtype-specific modulation of excitatory and inhibitory synaptic inputs in the rat brainstem. J. Physiol. 558, 745–757.

Webster, C.M., Hokari, M., McManus, A., Tang, X.N., Ma, H., Kacimi, R., Yenari, M.A., 2013. Microglial $P2Y_{12}$ deficiency/inhibition protects against brain ischemia. PLoS One (Electron. Resour.) 8, e70927.

Weisman, G.A., Ajit, D., Garrad, R., Peterson, T.S., Woods, L.T., Thebeau, C., Camden, J.M., Erb, L., 2012a. Neuroprotective roles of the $P2Y_2$ receptor. Purinergic Signal 8, 559–578.

Weisman, G.A., Camden, J.M., Peterson, T.S., Ajit, D., Woods, L.T., Erb, L., 2012b. P2 receptors for extracellular nucleotides in the central nervous system: role of P2X7 and $P2Y_2$ receptor interactions in neuroinflammation. Mol. Neurobiol. 46, 96–113.

Weisman, G.A., De, B.K., Friedberg, I., Pritchard, R.S., Heppel, L.A., 1984. Cellular responses to external ATP which precede an increase in nucleotide permeability in transformed cells. J. Cell Physiol. 119, 211–219.

Weisman, G.A., Woods, L.T., Erb, L., Seye, C.I., 2012c. P2Y receptors in the mammalian nervous system: pharmacology, ligands and therapeutic potential. CNS Neurol. Disord. Drug Targets 11, 722–738.

Willuweit, A., Velden, J., Godemann, R., Manook, A., Jetzek, F., Tintrup, H., Kauselmann, G., Zevnik, B., Henriksen, G., Drzezga, A., Pohlner, J., Schoor, M., Kemp, J.A., von der Kammer, H., 2009. Early-onset and robust amyloid pathology in a new homozygous mouse model of Alzheimer's disease. PLoS One (Electron. Resour.) 4, e7931.

Woods, L.T., Camden, J.M., Batek, J.M., Petris, M.J., Erb, L., Weisman, G.A., 2012. P2X7 receptor activation induces inflammatory responses in salivary gland epithelium. Am. J. Physiol. Cell Physiol. 303, C790–C801.

Wyss-Coray, T., 2006. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat. Med. 12, 1005–1015.

Yates, S.L., Burgess, L.H., Kocsis-Angle, J., Antal, J.M., Dority, M.D., Embury, P.B., Piotrkowski, A.M., Brunden, K.R., 2000. Amyloid β and amylin fibrils induce increases in proinflammatory cytokine and chemokine production by THP-1 cells and murine microglia. J. Neurochem. 74, 1017–1025.

Yu, N., Erb, L., Shivaji, R., Weisman, G.A., Seye, C.I., 2008. Binding of the $P2Y_2$ nucleotide receptor to filamin A regulates migration of vascular smooth muscle cells. Circ. Res. 102, 581–588.

Please cite this article in press as: Woods, L.T., et al., Purinergic receptors as potential therapeutic targets in Alzheimer's disease, Neuropharmacology (2015), http://dx.doi.org/10.1016/j.neuropharm.2015.10.031