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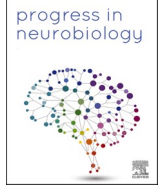
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Purinergic-associated immune responses in neurodegenerative diseases

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ABSTRACT

The chronic activation of immune cells can participate in the development of pathological conditions such as neurodegenerative diseases including Alzheimer's disease (AD), Multiple Sclerosis (MS), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS).

In recent years, compelling evidence indicates that purinergic signaling plays a key role in neuro-immune cell functions. The extracellular release of adenosine 5'-triphosphate (ATP), and its breakdown products (ADP and adenosine) provide the versatile basis for complex purinergic signaling through the activation of several families of receptors. G-protein coupled adenosine A_{2A} receptors, ionotropic P2X and G-protein coupled P2Y receptors for ATP and other nucleotides are abundant and widely distributed in neurons, microglia, and astrocytes of the central nervous system as well as in peripheral immune cells. These receptors are strongly linked to inflammation, with a functional interplay that may influence the intricate purinergic signaling involved in inflammatory responses.

In the present review, we examine the roles of the purinergic receptors in neuro-immune cell functions with particular emphasis on A_{2A}R, P2X4 and P2X7 and their possible relevance to specific neurodegenerative disorders. Understanding the molecular mechanisms governing purinergic receptor interaction will be crucial for advancing the development of effective immunotherapies targeting neurodegenerative diseases.

1. Introduction

Immune responses mediate tissue homeostasis in the healthy brain. Once an inflammatory stimulus has occurred, microglia and astrocytes in the central nervous system (CNS), and T-cells and macrophages at the periphery become active players in the modulation of the immune response promoting tissue repair (Boillée, 2022; Yang et al., 2020). However, chronic activation of these cells in response to injuries, infections, or toxic metabolites may become detrimental (Ghosh et al., 2021; Liu and Wang, 2017; Ransohoff et al., 2015). Prolonged activation of the immune system leads to a dysregulated response in which the release of inflammatory factors becomes toxic for neurons, promoting cell death and tissue damage, which in turn aggravates the disease prognosis (Cianciulli et al., 2020; Ghosh et al., 2021).

Neurodegeneration is tightly linked to an overactivity of immune cells. A large body of evidence suggests that chronic immune reactivity favors the onset and progression of many neurological disorders such as

Alzheimer's Disease (AD), Multiple Sclerosis (MS), Parkinson's disease (PD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS), in both mouse models and humans (Ghosh et al., 2021; Liu and Wang, 2017; Troncoso-Escudero et al., 2018),

Among the immune cells, a specific state of microglia cells has been described at sites of neurodegeneration in mouse models and human patients, called disease-associated microglia (DAM). DAMs are a subset of microglia cells which might play a protective role in diseases such as AD and ALS (Deczkowska et al., 2018). Indeed, DAMs have a unique transcriptional and functional signature including the expression of TREM2 receptor, which is a critical regulator of DAM activation and homeostasis (Keren-Shaul et al., 2017). Along the degenerative process, DAMs showed an increase in lipidic metabolism and phagocytic related genes, which may be crucial steps influencing the microglia states and functioning (Carver et al., 2023; Keren-Shaul et al., 2017).

The cross-talk between the CNS and the immune system is coordinated by an extensive network of neuromodulators/proteins and their

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respective receptors that allow cell-to-cell communication (Kölliker-Frers et al., 2021). Alterations of these interactions might therefore affect the correct functioning of the immune system (Dantzer, 2018; Hodo et al., 2020).

In this context, purinergic signaling has recently emerged as an important target in the control of immune responses. Adenosine 5'-triphosphate (ATP), the main fuel of cells, is essential for numerous physiological processes that require energy such as plasma membrane active transport or muscle contraction (Dunn and Grider, 2023). Moreover, ATP is also released into the extracellular space acting as a cell-to-cell signaling molecule in different tissues in both peripheral and CNS (Burnstock, 2006). Within cells, ATP concentration in basal conditions is maintained in the range of 1–10 mM. However, the presence of ATP is variable among the body regions and cells, depending on their energy needs. In the brain, intracellular ATP concentration ranges from 1.5 and 4.1 mM (Greiner and Glonek, 2021). Neurons exhibit ATP levels of 2–2.6 mM (Pathak et al., 2015; Toloe et al., 2014) while glial cell concentrations are around 2.8 mM (Pathak et al., 2015). In homeostatic conditions, extracellular ATP is present at low concentrations (1–10 nM) (Burnstock, 2006; Duveau et al., 2020; Trautmann, 2009). The maintenance of ATP levels is required to ensure cellular homeostasis (Dunn and Grider, 2023). Following stress, injury or cell death, ATP stored in

the cytoplasm is released outside of the cells, increasing the extracellular ATP concentration from the nanomolar up to the micromolar range. In mammalian organisms, high amounts of extracellular ATP are detected, as molecules released by damaged cells (DAMPs) activate the immune system. Moreover, released ATP is rapidly hydrolyzed by several ectonucleotidases such as CD39 and CD73 into adenosine diphosphate (ADP), adenosine monophosphate (AMP), or adenosine (Zimmermann, 2021). Regarding the mechanisms, the effect of exogenous ATP and its breakdown products is mediated by the activation of plasma membrane receptors named purinergic receptors (Di Virgilio et al., 2017). Purinergic signaling has been largely involved in the regulation of different physiological and pathological activities acting as neurotransmitters, or promoters of inflammation by attracting inflammatory cells (Dou et al., 2018; Grenz et al., 2011).

Purinergic receptors are widely distributed through the brain and body. They are found in pre- and post-synaptic neurons, astrocytes, microglia, and in peripheral cells such as macrophages and lymphocytes (Burnstock and Boeynaems, 2014). Activation of these receptors induces various effects depending on the cell-type where they are expressed (Chitnis and Weiner, 2017; Fiebich et al., 2014; Idzko et al., 2014; Soni et al., 2019) (Fig. 1). Moreover, their extended distribution suggests a complex and variable effect among cells and brain regions (Tóth et al.,

	A2A	P2X4	P2X7
Neurons	Neurotransmitter release, BDNF release, synaptic excitability and plasticity (Temido-Feirera et al., 2020; Carvalho et al., 2019; Cunha, 2016)	Influx of Ca ²⁺ , increase of neurotransmitter release, modulation of synaptic activity and plasticity (Bertin et al., 2021; Vavra et al., 2011; Pankratov et al., 2002)	Limited evidences of P2X7 in neurons (Illes et al., 2017; Miras-Portugal et al., 2017)
Astrocytes	GABA and glutamate uptake. Promotes inflammation (Paiva et al., 2019; Liddelow et al., 2017; Ferreira et al., 2013; Matos et al., 2012; Matos et al., 2013)	Limited evidences of P2X4 in astrocytes	Chemokines release (Carvalho et al., 2021; Martin et al., 2019)
Microglia	Modulation of inflammation, proliferation and morphology (Navia et al., 2020)	Regulation of microglia activation and migration Release of cytokines, IL-1β, BDNF, IL-18 or TNF-α (Khir et al., 2021; Montilla et al., 2020; Nguyen et al., 2020; Stokes et al., 2017)	IL-1β release, phagocytosis and regulation of ROS release Chemokines release (Carvalho et al., 2021; Martin et al., 2019; Parvatheni et al., 2003)
Oligodendrocytes	Oligodendrocytes differentiation (Coppi et al., 2015)	Oligodendrocytes differentiation (Zabala et al., 2018)	Evidence of P2X7 in oligodendrocytes Physiological role unknown (Kaczmarek-Hajek et al., 2018)
Peripheral cells	Endothelial cells	Endothelial cells	macrophages
	BBB integrity and vasodilatation (Wu et al., 2022; Hurtado-Alvarado et al., 2016; Kim et al., 2015)	Regulation of blood vessel tone and shear stress responses (Ozaki et al., 2016) neutrophils and macrophages Release of IL-1β and IL-18 (Kanellopoulos et al., 2021)	Phagocytosis, IL-1β release and pyroptosis (Di Virgilio et al., 2017)

Fig. 1. Summary of the respective functions of A2A, P2X4 and P2X7 reported in the CNS (neurons and glia) and in peripheral cells (endothelial cells, macrophages and neurotrophils).

2019). ATP activates P2 receptors which are divided into ligand-gated ion channels (P2X) and G-protein coupled receptors (P2Y) (Z. Huang et al., 2021; Tóth et al., 2019). On the other hand, adenosine activates P1 receptors, coupled to G proteins (Huang et al., 2021; Tóth et al., 2019).

In physiological conditions, it was shown that purinergic signaling is involved in synaptic transmission, neuromodulation, neuro-immune crosstalk, cell growth and differentiation, regulation of blood vessel tone, and muscle contraction (Gordon, 1986). In vitro, the pathological deregulation of these nucleotides can trigger a wide range of events, from oxidative stress to excitotoxicity and cell death, contributing to both onset and exacerbation of inflammatory processes (Chitnis and Weiner, 2017; Soni et al., 2019; Tóth et al., 2019). Previous studies described purinergic signaling involvement in numerous pathologies, including neurodegenerative diseases (Tóth et al., 2019).

In this review, we focus on the A_{2A}, P2X₄, and P2X₇ purinergic receptors, which are essential for microglia-mediated immune responses and play significant roles in neuroimmune modulation during neurodegenerative diseases. In addition, we further discuss the potential clinical implications of their modulation in the context of chronic immune cells activation.

Due to its expression and its major roles in the neuronal function but also in the glial cells such as astrocytes and microglia, A_{2A}R is known to induce a fine regulation of parenchyma homeostasis. Numerous studies concerning neurodegenerative diseases, epilepsy or psychiatric disorders, highlight major alterations in the expression and activity of this receptor, closely linked to dysfunction of neuroinflammatory processes (Launay et al., 2023; Moreira-de-Sá et al. 2021; Kaster et al., 2015; Bartoli et al., 2020; Canas et al., 2018). Moreover, P2X₄ expression in neurons and microglia in the CNS as well as in peripheral cells along with its high affinity for ATP and high calcium permeability makes this receptor a key modulator of glia and neurons at both, early and late disease stages (Andries et al., 2007). Finally, P2X₇ is known to be a sensor of high amount of ATP and its activation is involved in several physiological and pathological processes: phagocytosis, activation of the inflammasome NLRP3, release of pro-inflammatory mediators and cell death (Kanellopoulos et al., 2019).

Interestingly, A_{2A}, P2X₄ and P2X₇ receptors can exert beneficial and harmful effects during the disease progression. Dual roles of these purinergic receptors have been observed in mice models of AD, HD or ALS (Andries et al., 2007; Apolloni et al., 2013, 2014; Bertin et al., 2021; Du et al., 2022). This paradox may result from complex receptor interactions and their diverse roles in immune responses, neurotransmitter release and neuronal signaling which are not yet fully understood. (Cunha, 2016; Vavra et al., 2011). Other purinergic receptors like P2Y₆, P2Y₁₂ or A₃ expressed in microglia and involved in anti-inflammatory processes may also contribute to degenerative diseases, but information about their roles is still limited (Moore et al., 2015; Puigdemívol et al., 2021).

2. A_{2A} receptor

Adenosine is an important neuromodulator whose primary function is to control neuronal excitability (Agostinho et al., 2020; Cunha, 2016). Adenosine acts through four G protein-coupled receptors (GPCRs): A₁, A_{2A}, A_{2B} and A₃. The A₁ and A₃ receptors are coupled to inhibitory G proteins, thereby inhibiting adenylate cyclase and reducing the intracellular level of cyclic AMP (cAMP). Conversely, the A_{2A} and A_{2B} receptors are coupled to an excitatory G protein which activates adenylate cyclase, increasing cAMP intracellular levels. However, the effects of adenosine in the brain are mainly due to the A₁ and A_{2A} receptors which are the main adenosine receptors found in the CNS (Stockwell et al., 2017). A₁R is homogeneously expressed in the brain while A_{2A}R is particularly enriched within the striatum even also present, at lower levels, in the hippocampus and the cortex (Cellai et al., 2018). A₁ and A_{2A} receptors are localized pre- and post-synaptically at glutamatergic synapses (Rebola et al., 2003; Rebola et al., 2005), but also GABAergic,

adrenergic, cholinergic, dopaminergic and serotonergic neurons (Rebola et al., 2005a, 2005b; Schiffmann et al., 2007; Tetzlaff et al., 1987). Moreover, these receptors are expressed by glial cells, astrocytes and microglia, and endothelial cells (Agostinho et al., 2020; Cunha, 2016). Together, in physiological conditions, A₁ and A_{2A} receptors fine-tune cerebral homeostasis.

2.1. Neuronal regulation of synaptic signaling by adenosine

One of the main roles of adenosine receptors is the fine regulation of signal transmission and synaptic plasticity of the neuronal networks (Borea et al., 2018). In that way, A₁ and A_{2A} receptors control, on one hand, the release of neurotransmitters at the pre-synaptic level and, on the other hand, post-synaptic gating. In basal conditions, A₁R has an inhibitory tonic effect on synaptic transmission, mediated by pre-synaptic receptors preferentially activated by low levels of extracellular adenosine (Fredholm et al., 2005; Rebola, Rodrigues, et al., 2005). However, during neuronal stimulation, adenosine levels rise due to the synaptic release of ATP and its dephosphorylation by ectonucleotidases, which activates pre-synaptic A_{2A}R favoring glutamate release, and post-synaptic A_{2A}R, that will favor memory encoding and long-term plasticity in the hippocampus (Augusto et al., 2013; Cunha, 2016; Rebola et al., 2008). At the pre-synaptic level, A_{2A}R indeed promotes the release of glutamate by increasing calcium signaling allowing vesicles to release their content into the synaptic cleft (Lopes et al., 2002; Marchi et al., 2002). This pre-synaptic activity of A_{2A}R can relate to its ability to heterodimerize with inhibitory receptors such as the A₁ receptor but also the cannabinoid receptor CB₁ to reduce their inhibitory effects (Ciruela et al., 2006; Ferreira et al., 2015). Other studies suggest that, at the post-synaptic level, A_{2A}R can modulate the function of other receptors, such as the glutamatergic receptors mGluR5 and NMDAR. Indeed, several studies showed a positive impact of A_{2A}R on NMDAR signaling after its colocalization with mGluR5 (Domenici et al., 2004; Krania et al., 2018; Rodrigues et al., 2005; Sarantis et al., 2015; Tebano et al., 2005). Recent *in vitro* studies support that there could be a direct and physical interaction between A_{2A}R and NMDAR (Franco et al., 2020) supporting the ability of A_{2A}R to tune glutamatergic signaling, synaptic plasticity and neuronal networks (Rebola et al., 2008; Temido-Ferreira et al., 2020; Viana da Silva et al., 2016). In addition, it was highlighted that A_{2A}R can directly promote Brain-Derived Neurotrophic Factor (BDNF) signaling in physiological conditions, can through transactivation of its cognate tropomyosin-related kinase (TrkB) receptor. BDNF is essential for the facilitation of synaptic transmission and the regulation of long-term (LTP) processes.

2.2. Glial-based synaptic regulations by adenosine

Adenosine is also engaged in the control of physiological plasticity mediated by glial cells present at the tripartite synapse. Indeed, during neuronal activation, microglia cells release small amounts of ATP, and astrocytes, in turn, amplify this release. This allows the reinforcement of the signal transmission at the synapse by A_{2A}R activation but also, maintain the tonic inhibitory role of A₁R on the surrounding synapses (55). This regulation of microglial and astrocyte via adenosine signaling allows then network coordination and fine the regulation of basal synaptic transmission as well as LTP and LTD processes via A₁ and A_{2A} receptors (Pascual et al., 2005, 2012; Panatier et al., 2011).

Expression of A_{2A}R by glial cells can also directly modulate their activity and plasticity, in particular by gating the levels of extracellular neurotransmitters such as glutamate or GABA in the synaptic cleft. Indeed, A_{2A}R inhibits glutamate reuptake through an inhibitory action on astrocytic glutamatergic transporters (GLAST, GLT1) (Matos et al., 2012a, 2012b, 2013). At the same time, A_{2A}R improves the reuptake of GABA present in the extracellular environment via GABAergic transporters (Cristóvão-Ferreira et al., 2013). This suggests that adenosine strongly impacts excitatory/inhibitory synaptic balance through glial

cell-based mechanisms. However, the dynamics and molecular mechanisms underlying these effects remain poorly understood.

Moreover, it was shown that A_{2A}R can heterodimerize with other receptors such as the dopaminergic D₂ receptor or the oxytocin OT receptor where it can inhibit their negative modulation of glutamate release by astrocytes (Amato et al., 2022; Cervetto et al., 2017).

Besides their physiological role in synaptic plasticity, adenosine and its receptors have gained interest in the studies of neurodegenerative diseases, notably through the regulation of glial cells.

3. P2X4 receptor

P2X4 receptor (P2X4) is an ionotropic receptor activated by extracellular ATP. Once activated, the transmembrane pore of P2X4 allows the influx of Ca²⁺ and Na⁺, which causes a membrane depolarization, and the efflux of K⁺ (Stokes et al., 2017). This Ca²⁺ influx triggers important downstream signaling pathways such as neurotransmitter release by neurons or the release of cytokines by microglia (Franco-Bocanegra et al., 2019; Li et al., 2011). P2X receptor family is composed of seven distinct subunits (P2X1–7). Structurally, functional receptors are formed by the association of three subunits, harboring a total of three ATP-binding sites. P2X4 can form homo- or hetero-trimers with other specific P2X subunits such as P2X2 or P2X6, resulting in different functional properties. Although P2X4 and P2X7 are widely co-expressed in various cell types, there are contradictory reports on the existence of P2X4/7 heteromers and their functional relevance (Craigie et al., 2013; Saul et al., 2013; Schneider et al., 2017).

In physiological conditions, P2X4 is constitutively internalized by the clathrin-dependent endocytosis system through the interaction between the adaptor protein complex 2 (AP2) and the non-canonical endocytosis motif in the C-tail of P2X4 (Bobanovic et al., 2002; Royle et al., 2005). As a result, P2X4 is mainly found intracellularly, retained in lysosomes ensuring its low expression at the cell surface (Duveau et al., 2020; Montilla et al., 2020; Suurväli et al., 2017). Within lysosomes, P2X4 extracellular domains face lysosomal luminal compartment, allowing a functional binding of the lysosomal ATP (Zhang et al., 2007). Moreover, P2X4 is protected from proteolysis by its glycosylation (Suurväli et al., 2017). Thus, intracellular P2X4 can be functional and may regulate endo-lysosomal membrane fusion via Ca²⁺ dependent activation of calmodulin, a Ca²⁺ sensor protein found in the cytoplasm that controls different regulatory processes within cells (Huang et al., 2014). Recently, Sin and colleagues have shown that P2X4 is involved in the enlargement of lysosomes and their redistribution towards cell periphery (Tan et al., 2021). In pathological context, the lysosomal activity of P2X4 has been related to breast cancer progression (Chadet et al., 2022) and neurodegenerative disorders such as PD (Zhang et al., 2021).

Within the CNS, P2X4 is found widely but sparsely expressed in both neurons and glial cells. The functional relevance of P2X4 has already been demonstrated in neurons and microglia in physiological and pathological conditions (Bertin et al., 2021; Cham et al., 2006; Montilla et al., 2020; Stojilkovic and Zemkova, 2013; Xu et al., 2016). Few studies have detected P2X4 expression in astrocytes and oligodendrocytes by immunostaining, however its functional role remains to be determined (Lalo et al., 2008; Montilla et al., 2020). Outside the nervous system, P2X4 is expressed by other cell types such as macrophages, endothelial and epithelial cells (Suurväli et al., 2017).

3.1. Neuronal role of P2X4

P2X4 expression in neurons has first been described in rat brain in 1996 (Seguela et al., 1996; Soto et al., 1996). Later, P2X4 has been found to be expressed in extensive brain regions, including neurons from the dentate gyrus, CA1/CA3 (Soto et al., 1996), cortex (Lalo et al., 2007), pontine nucleus, striatum, and substantia nigra (Amadio et al., 2007). At the sensory level, neuronal P2X4 expression has been described in the trigeminal nerve, and in the vestibular (Ito et al., 2010) and nodose

ganglions (Tan et al., 2009), somatosensory cortex (Lalo et al., 2007), and spinal cord (Kobayashi et al., 2005). Moreover, P2X4 is widely expressed by many types of excitatory and inhibitory neurons, including pyramidal neurons, Purkinje cells, granule cells (Soto et al., 1996), GABAergic spiny neurons and interneurons, bipolar cells, supraoptic and spinal cord neurons (Kobayashi et al., 2005). Within these cells, P2X4 is localized in both pre- and post-synaptic terminals. Due to this wide distribution, P2X4 has been implicated in both physiological and pathological functions in the CNS.

Physiologically, P2X4 is involved in synaptic signaling and the modulation of neurotransmission. At the pre-synapse, P2X4 plays a role in the release of glutamate in sensory neurons (Gu and MacDermott, 1997). In the hypothalamus, the activation of pre-synaptic P2X4 has been related to the release of glutamatergic and GABAergic neurotransmitters (Vavra et al., 2011). On the other hand, post-synaptic P2X4 receptors can modulate synaptic transmission and plasticity in different brain areas. Electrophysiological recording in CA1 pyramidal neurons from hippocampal slices showed that the blockade of P2X4 facilitates the induction of LTP by high frequency stimulation. Post-synaptic P2X4 can affect LTP likely via Ca²⁺-dependent inactivation of NMDA receptors. The entry of Ca²⁺ in the cell through presynaptic P2X4 would also trigger vesicular release of neurotransmitter, thus controlling synaptic efficiency (Pankratov et al., 2002). In contrast, the potentiation of P2X4 using the positive allosteric modulator ivermectin, which acts by increasing the function and/or cell surface expression of P2X4, enhanced LTP in CA1 neurons in wild-type mice but not in mice lacking P2X4 (Sim et al., 2006). Nevertheless, the specific contribution of P2X4 in synaptic transmission is generally marginal and even controversial in accordance with the low surface expression of this receptor in basal conditions (Boué-Grabot and Pankratov, 2017). Interestingly, a crosstalk between P2X4 and GABA_A receptors (GABA_{AR}) has been proposed in which, using co-immunoprecipitation and pull-down assays, authors revealed the interaction between both receptors. When increasing P2X4 at the cell membrane using a competitive peptide blocking its internalization, the crosstalk between post-synaptic P2X4 and GABA_{AR} receptors in hypothalamic neurons downregulates inhibitory GABAergic synaptic currents (Jo et al., 2011). An explanation may be that the synaptic activity of P2X4 depends critically on the receptor trafficking between the intracellular space and the cell membrane (Bertin et al., 2021; Khakh & North, 2006). When increasing P2X4 at the cell membrane using an internalization-defective P2X4 knockin (P2X4KI) mice, P2X4 was shown to alter NMDAR-dependent LTP and LTD plasticity at CA1 excitatory neurons without affecting basal excitatory transmission (Bertin et al., 2021). Thus, P2X4 may modulate hippocampal plasticity by modulating NMDA receptor function. Indeed, a physical interaction between P2X4 and NMDAR induces the current inhibition of NMDAR *in vitro* (Rodríguez et al., 2020). Apart from these effects induced by the release of ATP by neurons, astrocyte-derived ATP can also activate postsynaptic P2X and induce long-lasting changes at excitatory synapses (Gordon et al., 2005). Calcium entry through postsynaptic P2X4 activated by glial ATP induces synaptic depression in the hippocampus by altering surface trafficking of synaptic AMPAR (Pougnat et al., 2014). At inhibitory synapses, a similar action of astrocytic ATP modulates phasic and tonic GABAergic inhibition by down-regulating GABA_{AR} in the cortex (Lalo et al., 2014). In a model of postoperative hyperalgesia, P2X4 increases the AMPAR subunit GluA1 in spinal dorsal horn neurons in a BDNF-TrkB dependent manner, thus modulating AMPAR-mediated excitatory postsynaptic currents (Fu et al., 2021).

It is important to note that the role of P2X4 in neurons is complex and can vary depending on the neuronal network involved, the brain region and the physiological context. Further studies need to better clarify how P2X4 modulates synaptic transmission, addressing its potential implication during pathological inflammation.

3.2. The role of P2X4 within microglia

In addition to neurons, P2X4 is expressed in microglia. While a low P2X4 density is found in resting microglia, a clear *de novo* P2X4 expression has been observed in reactive microglia in many inflammatory-related diseases including neuropathic pain induced by nerve injury (Tsuda et al., 2003; Ulmann et al., 2008), ischemia (He et al., 2022) and status epilepticus (Ulmann et al., 2013).

Several extracellular factors have been proposed to regulate P2X4 expression in microglia in chronic pain context, such as the chemokine (C-C motif) ligand 21 (CCL21), the colony stimulating factor 1 (CSF1) and the fibronectin (Kohno and Tsuda, 2021). Likewise, transcriptional factors such as IRF8 and IRF5 may promote P2X4 expression within microglia (Kohno and Tsuda, 2021). Considering the gender, controversial results have been found on sexual dimorphisms in microglial P2X4 driving inflammatory functions (Mapplebeck et al., 2016; Nguyen et al., 2020). However, a recent study showed that microglial P2X4 plays a key and similar role in chronic pain in both male and female (Gilbert et al., 2023).

Generally, P2X4 activation in reactive microglia promotes detrimental effects (Ulmann et al., 2008; He et al., 2022). Nevertheless, P2X4 is also involved in physiological functions such as microglia motility, chemotaxis, phagocytosis and cytokines release (Ohsawa et al., 2007; Franco-Bocanegra et al., 2019; Gofman et al., 2014; Illes et al., 2020; Li et al., 2011; Ohsawa and Kohsaka, 2011). Once activated by extracellular ATP, P2X4 induces microglia motility by increasing intracellular Ca^{2+} leading to AKT phosphorylation in a PI3K dependent manner, ultimately inducing cytoskeletal rearrangements (Franco-Bocanegra et al., 2019; Horvath and DeLeo, 2009). One study has found that the potentiation of microglia migration using morphine was strongly impaired when using TNP-ATP [2',3'-O-(2,4,6-trinitrophenyl)-ATP], a P2X4 antagonist. Interestingly, P2X4 was upregulated when microglia were treated with morphine (Horvath and DeLeo, 2009). Later, it was shown that the interaction between P2X4 and P2Y12 receptors is involved in ATP-induced microglial migration (Illes et al., 2020; Ohsawa and Kohsaka, 2011).

Following an inflammatory stimulus, P2X4 has been related to microglial cytokines release, and ATP-induced calcium influx, among others. After 24 hours of lipopolysaccharide (LPS) stimulation of microglial activation, Nguyen and collaborators have shown a decreased activity of P2X4, leading to the reduction of ATP-induced calcium influx. Importantly, microglial expression of the voltage-gated potassium channel Kv1.3 is required for activation and its associated inflammatory responses. After LPS exposure, P2X4 downregulation in microglia inhibits Kv1.3 channels, alleviating the inflammatory phenotype (Nguyen et al., 2020). Opposite to this result, other groups have found that cultured or in vivo microglia stimulated with LPS led to an upregulation of P2X4 expression accompanied by a transient increase of P2X4-mediated inward currents within microglia (Raouf et al., 2007; Vázquez-Villoldo et al., 2014; Bertin et al., 2021). A significant amount of P2X4 protein stays in intracellular compartments within microglia, pointing out a possible intracellular role for P2X4 receptor in microglial response (Raouf et al., 2007).

Moreover, P2X4 has been related to microglial release of TNF- α and IL-1 β cytokines (Li et al., 2011). Interestingly, blocking of P2X4 function during hypoxic conditions with 2', 3'-O-(2, 4, 6-Trinitrophenyl) adenosine 5'-triphosphate (TNP-ATP) suppressed the production of the above-mentioned cytokines. Controversial results have been found regarding the role of P2X4 on microglia activation. Zabala and collaborators found that the upregulation of P2X4 favors a switch to an anti-inflammatory phenotype within microglia in a model of multiple sclerosis (MS) (Zabala et al., 2018). Controversially, an increase of P2X4 expression in microglia has also been associated with a neurodegenerative phenotype. Using spatial transcriptomics in AD human and mice models, an increase of mRNA P2X4 expression was found in plaque-associated DAM cells (Hua et al., 2023).

Whereas these studies highlighted the role of P2X4 controlling microglial phenotype, several ones could not find any effect when modulating this receptor. Using ionized calcium binding adaptor molecule 1 (Iba1) staining within the spinal cord of P2X4KO mice (Ulmann et al., 2008) or P2X4KI mice (Gilbert et al., 2023) after peripheral nerve injury, the authors found that deletion or surface increase of P2X4 did not change microglial activation observed in neuropathic pain conditions. In a model of epilepsy, using P2X4KO mice, an attenuation of microglial reactivity was accompanied by a decrease of distinct hallmarks of microglia activation (Rassendren & Audinat, 2016). In addition, using an LPS-induced sepsis mouse model, deletion of P2X4 did not change microglia reactivity and LPS-driven transcriptomic remodeling. Overall, the role of P2X4 on the microglia activation is still controversial and highlights the functional diversity of microglial reactions.

Several signals such as MAPK/ERK, PKA/PKC and, AKT pathways and Ca^{2+} mobilization have been associated with P2X4 activation and functions in microglia (Franco-Bocanegra et al., 2019; Stokes et al., 2017) (Fig. 2). P2X4 also regulates the activation of the Nod-like receptor family protein 1 (NLRP1) and 3 (NLRP3) inducing Ca^{2+} influx during inflammation (Wang et al., 2021). These pathways have directly been involved in the microglial release of secretory molecules such as IL-1 β , BDNF, IL-18, iNOS or TNF- α (Khir et al., 2021; Montilla et al., 2020; Nguyen et al., 2020; Stokes et al., 2017). Concerning the BDNF signal, it is involved in shaping the crosstalk between neurons and the immune system. As for TNF- α and IL-1 β , its production was suppressed when P2X4 was blocked with TNP-ATP (Li et al., 2011). Indirectly, P2X4 is required for effective production of IL-1 β and IL-6, via the activation of P2X7 receptor (Stokes et al., 2017).

In pathological conditions, P2X4 upregulation in microglia is well known to be involved in neuropathic pain. In a mice model of neuropathic allodynia, the absence, or the blockade of P2X4 was sufficient to prevent tactile allodynia, a debilitating pain symptom (Tsuda et al., 2003; Ulmann et al., 2008). Regarding the mechanisms, it has been shown that P2X4 upregulation in spinal cord microglia induced the release of BDNF by these cells via p38MAPK. BDNF binds and activates TrkB receptors on the nociceptive spinal neurons which downregulates the $K^+ Cl^-$ cotransporter 2 (KCC2). KCC2 is a transporter involved in the maintenance of Cl^- gradients on GABAergic cells. Thus, BDNF-inducing downregulation of KCC2 reduces inhibitory currents within dorsal horn neurons, leading to spinal neurons hyperexcitability and mechanical hypersensitivity (Coull et al., 2005; Tsuda et al., 2003). Later studies have confirmed these results, showing that the pharmacological blocking of P2X4 can inhibit pain (Zhang et al., 2023). The present study highlights the importance of microglial functions in shaping neuronal activity.

Apart from neuropathic pain, the microglial role of P2X4 has been described in traumatic brain injury, migraine and neurodegenerative diseases, among others (He et al., 2022; Xu et al., 2022). After brain injury, P2X4 expression is found upregulated in microglia at the damaged area. He and colleagues demonstrated that the inhibition of P2X4 with the antagonist 5-(3-bromophenyl)-1,3-dihydro-2H-benzofuro [3,2-e]-1,4-diazepin-2-one (5-BDBD), significantly reduces neurological damage by decreasing inflammation and microglial apoptosis through the NLRP3 pathway (He et al., 2022). In a model of migraine, microglial P2X4 has been involved in migraine progression by promoting the synthesis and release of BDNF which contributes to central neuronal sensitization via ERK signaling (Long et al., 2018).

Taken together, these studies point toward an important role of microglial P2X4 in physiological and inflammatory responses in the CNS. P2X4 receptor might then represent an attractive therapeutic target to reduce neuroinflammation associated with detrimental functions of microglia. Since P2X4 expression at the cell surface is particularly sensitive to inflammatory stimuli, this receptor has been described in numerous neurodegenerative diseases involving neuroinflammation such as ALS, MS, PD and AD.

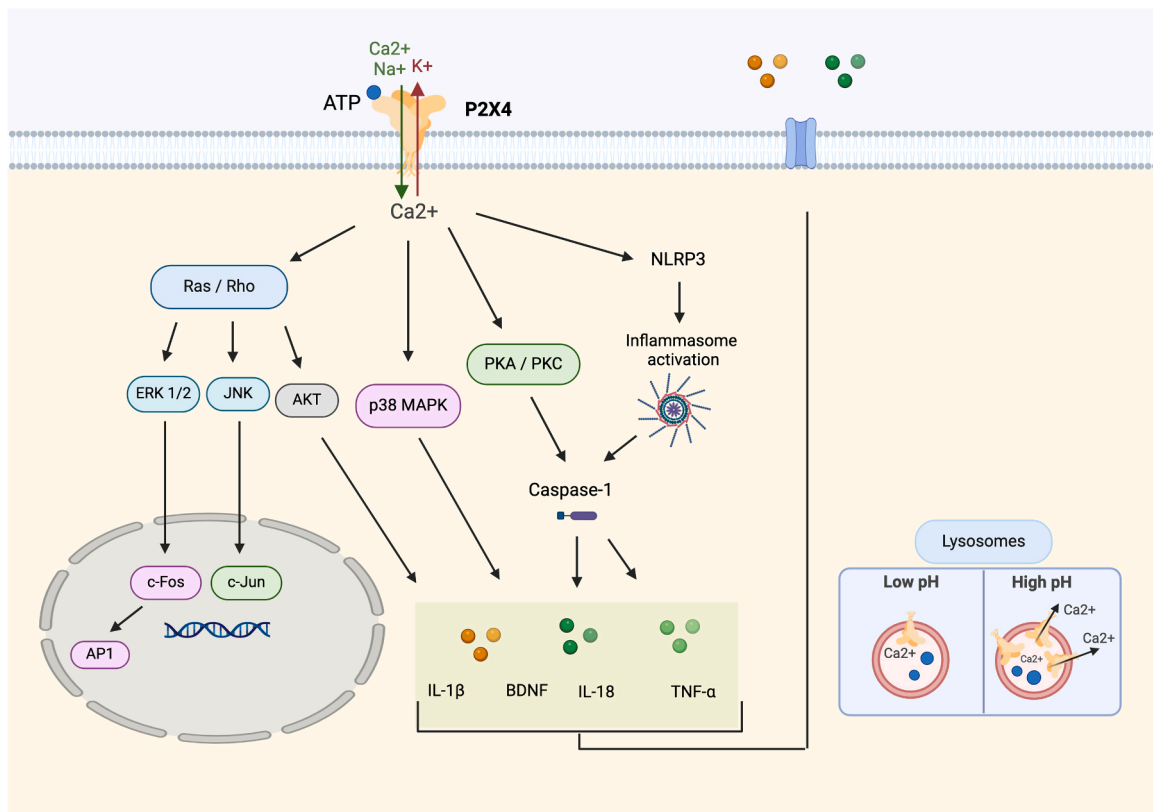


Fig. 2. Signaling pathways modulated by P2X4 receptor in microglia. Once activated by ATP, P2X4 allows the influx of Ca^{2+} , Na^{2+} and K^{+} . P2X4 activation has been related with Ras/Rho signaling and PKA/PKC (Long et al., 2018; Stokes et al., 2017), as well as with MAPK pathway activated via Ca^{2+} . These pathways have been directly involved with the release of secretory molecules such as IL-1 β , BDNF, IL-18 or TNF- α (Khiri et al., 2021; Montilla et al., 2020; Stokes et al., 2017). In addition, P2X4 within lysosomes is involved in cathepsin release and the activation of NLRP3 and the inflammasome signaling.

3.3. P2X4 in peripheral cells

P2X4 is expressed in several types of peripheral cells such as macrophages. Within these cells, P2X4 has been reported to contribute to the ATP-evoked Ca^{2+} influx (Layhadi and Fountain, 2017).

In pathological context, injection in control mice of ATP-primed macrophages into the paw was sufficient to elicit pain hypersensitivity while in P2X4KO mice there was no effect, showing the key role of P2X4 expressed by resident macrophages in inflammatory pain (Ulmann et al., 2010). Moreover, the interaction between P2X4 and P2X7 has been suggested to promote inflammation via Ca^{2+} influx and the release of proinflammatory cytokines such as IL-1 β and IL-18 (Kanellopoulos et al., 2021). In a model of chronic musculoskeletal pain, authors hypothesized that exercise could lead to the release of ATP, that in turn binds and activates P2X4, inducing hyperalgesia via IL-1 β release. Using a macrophage specific lentivirus, P2X4 blockade prevented hyperalgesia in musculoskeletal pain (Oliveira-Fusaro et al., 2020). In a model of glioma, P2X4 was found overexpressed in tumor associated macrophages. When silencing P2X4 within these cells, a decrease of glioma cells migration was observed, associated with a decrease of IL-1 β and IL-18 release by macrophages.

Apart from macrophages, P2X4 is abundant in epithelial and endothelial cells from salivary glands and bronchiolar epithelium. In vascular endothelial cells, P2X4 controls the vascular tone by regulating blood flow (Ozaki et al., 2016). During chronic arterial inflammation, endothelial P2X4 receptors regulate vascular remodeling (Fukuda et al., 2019; Yamamoto et al., 2006). Fukuda and collaborators suggested that P2X4 is required for inflammation, contributing to cerebral aneurysm formation and growth (Fukuda et al., 2019). Despite the numerous detrimental roles attributed to P2X4 during inflammatory conditions, P2X4 also have anti-inflammatory functions (Ozaki et al., 2016). By

blocking the expression of P2X4 in endothelial cells, Yamamoto and co-workers found a low Ca^{2+} influx and consequently, production of the vasodilator nitric oxide (NO). Indeed, P2X4KO mice showed higher blood pressure values and a decrease in both, the vessel dilation and its adaptive response to the blood flow (Yamamoto et al., 2006). Interestingly, the chronic elevation of blood pressure led to adverse glial activation and increased brain inflammatory factors (Bajwa and Klegeris, 2022). Hu and collaborators have found that P2X4 increases cardiac inotropy and that the overexpression of human P2X4 was protective against ischemic models of heart failure (Yang et al., 2004).

To conclude, P2X4 has also been found expressed in other peripheral cells such as eosinophils, which are cells that control immune homeostasis and contribute to tissue damage during autoimmune diseases, asthma, and infections. During allergic responses, P2X4 is overexpressed on circulating and activated cells. Hence, P2X4 may have a role on eosinophils once activated by extracellular ATP (Paalme et al., 2019).

4. P2X7 receptor

The purinergic receptor P2X7 (P2X7) is a non-selective ligand-gated ion channel belonging to the P2X ionotropic receptors family. It is encoded as a 595 amino-acid long monomeric protein by the *p2rx7* gene that assembles into a trimeric complex to form the functional P2X7 receptor. Each P2X7 subunit are composed of an ATP-binding large extracellular loop of about 300 amino acids, two transmembrane helices and two intracellular N- and C- termini (Surprenant et al., 1996). P2X7 possess a long C-Terminal chain of 239 amino acids, a structural feature that sets it apart from other receptors of the P2X family and that is necessary for the receptor functions (Surprenant et al., 1996). P2X7 properties and functions are unique among the P2X receptors. Unlike other receptors, P2X7 presents low affinity for ATP and is activated by

high extracellular ATP concentrations that are above homeostatic levels (EC 50 > 100 μ M). In addition, the signaling pathways triggered by P2X7 activation depend on the level of extracellular ATP and the duration of the stimulus. ATP binding to P2X7 induces a rapid influx of Ca^{2+} and Na^{+} and the efflux of K^{+} through the cell membrane (Di Virgilio et al., 2017). However, the prolonged exposure to ATP, instead of causing receptor desensitization, leads to the opening of a large pore permeable to molecules up to 900 Da (Di Virgilio et al., 2018; Falzoni et al., 1995) ultimately impairing cell ionic homeostasis and causing cell death (Surprenant et al., 1996; Virgilio et al., 1998). P2X7 is widely expressed by cells of the hematopoietic lineage in particular macrophages and monocytes but also lymphocytes and mast cells among many others. In the CNS, P2X7 is strongly expressed in microglia, but also in astrocytes, oligodendrocytes and Bergmann cells (Illes et al., 2012). However, neuronal expression of P2X7 is an intense subject of debate (Illes et al., 2017; Miras-Portugal et al., 2017; Kaczmarek-Hajek et al., 2018; Habbas et al., 2011). Using hybridation in situ, P2X7 was shown to be highly expressed in microglia, oligodendrocytes and neurons in rat brain sample (Yu et al., 2008a, 2008b) and in the CA3 region of the hippocampus in mice and humanized P2X7 mice (Martin et al., 2019; Metzger et al., 2017). In a recent study, using a transgenic reporter mice P2X7-eGFP and anti-P2X7 nanobodies, Kaczmarek et al., reported P2X7 expression in microglia, Bergmann glia and oligodendrocytes but not in neurons (Kaczmarek-Hajek et al., 2018).

P2X7 broad expression among many types of immune cells and its ability to be activated in response to high ATP levels make this receptor a central actor during inflammation.

4.1. P2X7 central role in inflammation

P2X7 is recognized as the main sensor of ATP during inflammation and many functions from cytokines production to cell death have been attributed to this receptor (Di Virgilio et al., 2017). The most described function of P2X7 is its essential role in the maturation and the release of IL-1 β through the activation of the NLRP3 inflammasome (Di Virgilio, 2007; Ferrari et al., 1997). A two-signal model has been proposed for the release of this cytokine. In a first step, stimulation of Toll-like receptors (TLRs) leads to the transcription and accumulation of pro-IL-1 β in the cytoplasm. In a second step, ATP-dependent stimulation of P2X7 triggers an efflux of K^{+} promoting the assembly of the NLRP3 inflammasome. Afterwards, NLRP3 activation leads to the cleavage of pro-caspase-1 to its active form caspase-1. Finally, pro-IL-1 β is processed by caspase-1 to its active form IL-1 β and released from the cell. Furthermore, caspase-1 will cleave gasdermin D (GSDMD), involved in programmed necrosis, releasing its N-terminal end capable of oligomerizing and forming pores in the plasma membrane. The formation of these pores induces a lytic and pro-inflammatory form of cell death called pyroptosis (He et al., 2015; Shi et al., 2015). The pore formed by the oligomerized N-Terminal end of GSDMD enables the release of mature IL-1 β in the extracellular space and the activation of further inflammatory processes. Extracellular release of IL-1 β can also be mediated by secretory lysosomes, exosomes and microvesicles (Giuliani et al., 2017).

4.2. The role of P2X7 in microglia

Activation of P2X7 on microglia triggers pro-inflammatory effects notably the release of cytokines and reactive oxygen species (Parvathani et al., 2003). P2X7-stimulated microglia release IL-1 β in the same way as macrophages by activating the NLRP3 inflammasome (Bianco et al., 2005). In addition, stimulation of microglial cells with ATP or BzATP can induce neurons death by releasing superoxide and nitric oxide (Skaper et al., 2006). P2X7 was reported to be involved in the release of several cytokines and chemokines, notably TNF α , IL-6, CCL2, CCL3 and CXCL2 (Kataoka et al., 2009; Martin et al., 2019; Carvalho et al., 2021; Shiratori et al., 2010; Suzuki, 2004). In case of neurodegenerative disease, ATP released by damaged neurons could activate

microglial P2X7 worsening the scenario by increasing the release of pro-inflammatory cytokines and reactive oxygen species which would aggravate neuronal death.

However, at homeostasis, P2X7 may have beneficial roles. Interestingly, in absence of ATP, P2X7 was reported to function as a scavenger receptor in macrophages and microglia (Gu and Wiley, 2018; Janks et al., 2018) by forming a complex with the non-muscle myosin IIA able to bind apoptotic cells allowing their phagocytosis (Gu et al., 2010). When ATP concentration is rising, macrophages phagocytosis is impaired by dissociation of this complex (Gu et al., 2010).

In the following parts, we will discuss how $\text{A}_{2\text{A}}\text{R}$, P2X4 and P2X7 contributes to neuro-immune processes in neurodegenerative diseases. Neurodegenerative diseases are characterized by a progressive loss of a target neuronal population in various structures involved in cognition, mobility, or coordination. Degeneration is exacerbated by a wide range of factors, including environmental and genetic, the main one being aging. Here we present the neurodegenerative diseases among which the $\text{A}_{2\text{A}}\text{R}$, P2X4 and P2X7 receptors have been the most studied.

5. Purinergic signaling in neurodegenerative diseases

5.1. Alzheimer's disease

Nearly 70 % of dementia cases are attributed to AD, affecting 35 million people worldwide in 2020 (OMS, 2020). Neuropathologically, AD is defined by the presence of two characteristic lesions: the extracellular accumulation of A β peptides into plaques; and the intraneuronal accumulation of hyperphosphorylated Tau proteins forming neurofibrillary tangles and referred to as Tau pathology (Buée et al., 2010; Sergeant et al., 2008). In AD patients, these lesions develop according to a defined hierarchical and stereotypical pattern defined by the Braak and Thal stages. Although the origin of the development of these lesions remains poorly understood, it has been shown that amyloid pathology preceded the spreading of Tau pathology (Trinh et al., 2022). A third component promotes the progression of the pathology: neuro-inflammation. As indicated above, in AD, the initial protective inflammatory response persists over time as an abnormal and chronic toxic neuro-inflammation through the persistent activation of glial cells, favoring the development of AD lesions (Laurent et al., 2018).

5.1.1. The role of $\text{A}_{2\text{A}}\text{R}$ in AD

Compelling evidence suggest that the $\text{A}_{2\text{A}}\text{R}$ can modulate AD acting on these three pathophysiological components. First, a 2017 study demonstrated a direct link between $\text{A}_{2\text{A}}\text{R}$ and AD by identifying a polymorphism in the *adora2a* gene which was associated with a decrease in the volume of the hippocampus, a key structure involved in the regulation of cognitive processes such as memory, which particularly degenerate in demented individuals (Horgusluoglu-Moloch et al., 2017). That said, how the neuronal and glial pools of the receptor are involved in AD development seems complex.

At the cellular level, several studies have demonstrated a gradual increase in the expression and density of $\text{A}_{2\text{A}}\text{R}$ in the neurons of the hippocampus in the elderly and AD patients, supporting a link between $\text{A}_{2\text{A}}\text{R}$ expression and the underlying pathology (Lopes et al., 1999; Orr et al., 2015; Temido-Ferreira et al., 2020). Interestingly, knowing the physiological role of neuronal $\text{A}_{2\text{A}}\text{R}$ in synaptic plasticity (see above), it seems that such receptor dysregulation is prone to strongly impact memory processes. It appears that the sole overactivation of neuronal $\text{A}_{2\text{A}}\text{R}$ expression is sufficient to promote memory impairments in rodents (Batalha et al., 2016; Temido-Ferreira et al., 2020). Moreover, such $\text{A}_{2\text{A}}\text{R}$ dysregulation is prone to favor synaptic loss in the context of AD (Carvalho et al., 2019). In particular, it seems that the neuronal $\text{A}_{2\text{A}}\text{R}$ upregulation changes the neuro-microglial signaling to favor the pruning of glutamatergic synapses, although the mechanism remains unclear yet (Carvalho et al., 2019). All these observations are in accordance with the beneficial impact of $\text{A}_{2\text{A}}\text{R}$ blockade (pharmacological or genetic) in

AD models developing amyloid or tau pathologies.

Besides neuronal receptors, A_{2A}R has also important roles in the context of neuroinflammatory processes, particularly thanks to its expression by microglial cells and astrocytes. During inflammatory processes, an increase of A_{2A}R density is observed within microglia and astrocytes as well as an increase in the levels of extracellular adenosine, allowing its activation (Cunha, 2016; Madeira et al., 2018; Zhao et al., 2017, 2019). In particular, A_{2A}R expression is increased in astrocytes of the hippocampus and cortex in AD patients (Angulo et al., 2003; Orr et al., 2015) as well as in microglia in some AD models (Lillo et al., 2022). At the astrocytic level, it has been demonstrated that the overexpression of A_{2A}R participates in the establishment of pro-inflammatory transcriptional dysregulations defined by an increase in reactivity markers such as GFAP, Vimentin and Timp1 as well as the pro-inflammatory marker IL1b (Paiva et al., 2019; Saha et al., 2020). Interestingly, A_{2A}R blockade controls astrogliosis and pro-inflammatory factors both *in vitro* and in a model of tauopathy, demonstrating the involvement of A_{2A}R in the regulation of inflammatory parameters related to AD (Brambilla et al., 2003; Laurent et al., 2016; Paiva et al., 2019). Moreover, in the context of AD, the lesions can directly modulate astrocytic functions. It has been interestingly demonstrated that Aβ inhibits the ability of astrocytes to recapture glutamate, an effect reverted following A_{2A}R blockade (Matos et al., 2012a, 2012b; Matos et al., 2013).

In the same range of idea, amyloid deposits impair the control of astrocyte-astrocyte communication through connexins 43 and release of ATP by these glial cells, effects reverted by A_{2A}R blockade (Dias et al., 2022; D. Madeira et al., 2021). These observations point towards the important role of astrocytic A_{2A}R dysregulation in the control of neurotransmitter dynamics in AD. Furthermore, astrocytic A_{2A}R may also act on the development of the pathology itself by decreasing the clearance of abnormally aggregated proteins. Indeed, overexpression of A_{2A}R by astrocytes alters the polarization of aquaporin 4 from the feet of the astrocytes, which are in contact with the blood-brain barrier (BBB), towards the soma, presumably preventing its essential role in the elimination of brain toxins (Iliff et al., 2012; Z.-A. Zhao et al., 2017). Overall, these observations likely explain the benefit afforded by astrocytic deletion of A_{2A}R towards memory impairments in a model of amyloidogenesis (Orr et al., 2015).

The role of microglial A_{2A}R in the context of AD remains largely unclear. In particular, the microglial functions of A_{2A}R would depend on the context and be particularly set by the extracellular concentrations of glutamate. At low glutamate concentrations of (0.1 mM), A_{2A}R activation promotes an anti-inflammatory microglial phenotype while at higher concentrations, it induces a pro-inflammatory phenotype (Du et al., 2022), characterized by a release of cytokines such as IFN-γ and TNF-α, IL1-β, the induction of oxidative stress through the release of ROS and NO but also by the activation of the NLRP3 inflammasome, recently involved in the development and spreading of amyloid and tau AD lesions (Heneka et al., 2013; Martí Navia et al., 2020; Rebola et al., 2011; Saura et al., 2005). Interestingly, inhibition of A_{2A}R signaling limits the activation of NLRP3 and the associated release of pro-inflammatory cytokines (Zhao et al., 2019). The dependence of A_{2A}R microglial function on extracellular glutamate supports that the latter may be intimately dependent on the synaptic and astrocytic A_{2A}R that set the release and reuptake of glutamate. Finally, A_{2A}R has been shown to play a role in the motility of microglia (Orr et al., 2009). Indeed, the microglia presents around amyloid plaques exhibit abnormal motility inducing an altered protective response towards the present lesions. The use of an A_{2A}R antagonist can partially restore microglial motility (Gyoneva et al., 2009, 2016). Altogether, these results demonstrate that dysregulation of A_{2A}R in the context of AD participates in neuronal, astrocytic, and microglial dysfunctions that promote the development of the pathology and the associated cognitive decline. These data also highlight the important of the A_{2A}R-based regulation into neuro-glial communication as well as a presumable functional link between the

different pools of cellular A_{2A}R in the degenerating brain (Fig. 3).

5.1.2. The role of P2X4 in AD

Microglial activation contributes to neuroinflammation and cognitive impairment in AD (Bajwa and Klegeris, 2022). *De novo* expression of P2X4 was found in plaques associated with microgliosis in AD human brains and mice models (Hua et al., 2023). In the APP/PS1 mice model of AD, blocking P2X4 expression did not affect plaque extension. However, it reversed the cognitive declines, improving topographic and spatial memory. Hua and colleagues showed that P2X4 is coexpressed with ApoE, a well-known AD risk factor, in Aβ plaques. Authors suggest that P2X4 may be related to the degradation of this protein during AD. It was proposed that P2X4 modulates the activity of cathepsin B within lysosomes, promoting ApoE degradation, altering Aβ peptide clearance by microglia, which might turn into memory deficits in APP/PS1 mice (Hua et al., 2023).

Apart from microglia, P2X4 expressed in neurons may play a further role in AD. An *in vitro* study showed that hippocampal neurons exposed to a toxic form of Aβ overexpressed P2X4 in cell bodies and neurites after 12 h of exposition. Authors found that the toxic form of Aβ was preventing P2X4 internalization through the caspase-3 cleavage of the C-terminal. Moreover, when overexpressing P2X4 in primary neurons, the noxious effect of Aβ was increased, while blocking P2X4 decreased neuronal death (Varma et al., 2009). The present findings strongly correlate the abnormal P2X4 trafficking with neuronal death in AD pathogenesis. Moreover, a possible cause to neuronal damages induced by Aβ may be a destabilization of calcium-permeable receptors such as NMDAR and voltage-operated calcium channels (VOCCs). Calcium dysregulation prolongs membrane depolarization, turning into an over activation of VOCCs. This feature has been associated with oxidative stress, mitochondrial dysfunction, and cell apoptosis during AD (Ge et al., 2022; Markesbery, 1997; Varma et al., 2009). In this sense, the study has involved the P2X4 receptor in the Aβ-inducing dysregulated calcium influx. Neurons overexpressing P2X4 exhibited exaggerated peak increases of cytosolic calcium in response to ATP and this influx was potentiated when adding Aβ. In contrast, decreasing P2X4 level promoted the opposite effects (Varma et al., 2009). P2X4 permeability to calcium may then contribute to Aβ-induced neuronal cell death.

Using the P2X4KI mice, which increases surface P2X4 expression by blocking its constitutive internalization either in all cells natively expressing P2X4 or selectively in excitatory forebrain neurons, Bertin and coworkers revealed that the specific increased surface density of P2X4 in forebrain excitatory neurons decreased anxiety-like behavior, and impaired memory processing as well as the activity-dependent synaptic plasticity phenomena in the hippocampus (Bertin et al., 2021).

Overall, these studies support that both neuronal and microglial P2X4 receptor may contribute to AD pathology (Bertin et al., 2021; Ge et al., 2022; Varma et al., 2009). P2X4 receptor may modulate microgliosis towards a beneficial phenotype in AD (Suurväli et al., 2017). On the other hand, neuronal P2X4 may have deleterious effects towards synaptic dysfunction and neuronal death associated to AD pathogenesis (Fig. 3).

5.1.3. P2X7 role in AD

Upregulation of P2X7 expression is observed in the brain of AD patients. Immunohistochemical analysis of AD brains revealed that P2X7 expression is increased near amyloid plaques and activated microglia (McLarnon et al., 2006). These results were subsequently confirmed by Martin and coworkers who also reported P2X7 expression by microglial cells and astrocytes in the brain from patients with AD (Martin et al., 2019). Likewise, P2X7 is co-localized with activated microglia in a rat model of AD induced by intrahippocampal injection of amyloid-β peptide (McLarnon et al., 2006). Similar results were observed in the Tg2576 transgenic mouse model of AD expressing the mutated human APP protein. In this model, P2X7 expression is upregulated in the hippocampus. In addition, P2X7 is expressed in area with a high density of

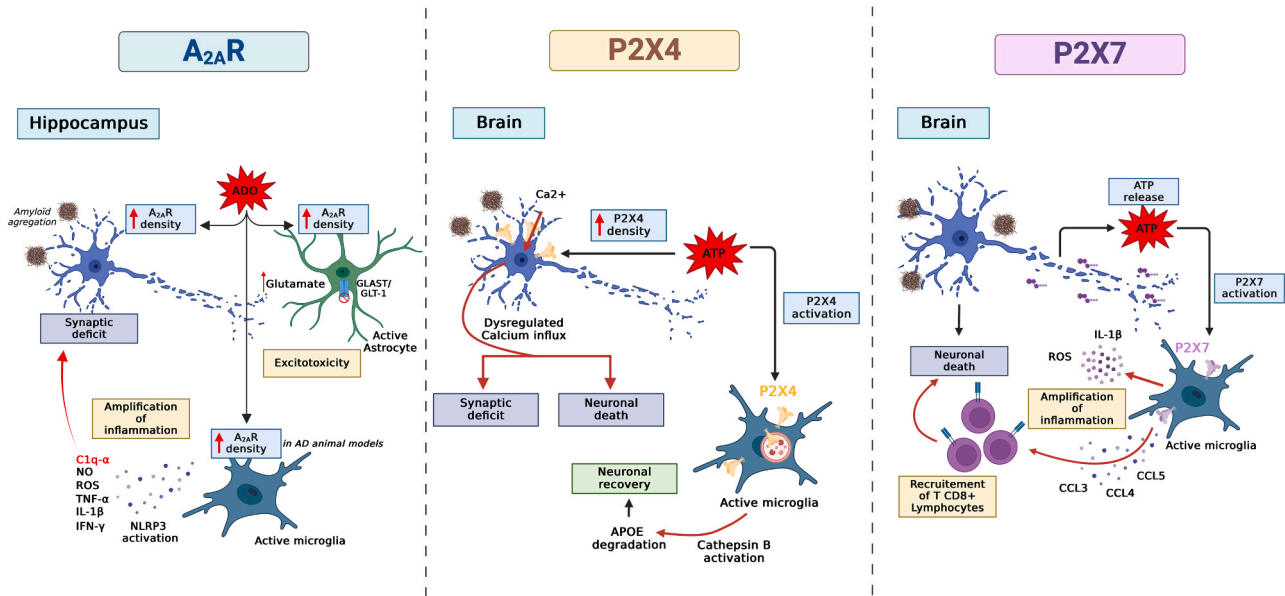


Fig. 3. Model of the roles of the purinergic receptors in Alzheimer's disease. In AD, astrocytes and neurons show an increase in A2AR density (this phenomenon is observed in the microglia of many mouse models of the pathology). This will cause an alteration in the extracellular balance of glutamate/GABA neurotransmitters by alteration of astrocyte reuptake via GLAST/GLT-1 transporters as well as the induction of microglial inflammation causing synaptic loss via the complementary protein C1q. On the other hand, ATP will bind P2X4 receptors in both microglia and neurons and P2X4 receptors in microglia. In microglia, P2X4 activation will promote Cathepsin B activity within the lysosomes, improving APOE degradation and thus, neuronal recovery. However, P2X4 activation in neurons has been related to Ca^{2+} cytotoxicity, leading to synaptic deficit and neuronal death. Further, ATP would also bind to P2X7 on microglia and induce the release of IL-1 β and reactive oxygen species therefore amplifying the neuroinflammation. In addition, microglial cells would release chemokines triggering the recruitment of pathogenic CD8+ T cells.

amyloid- β plaques and co-localize with activated microglia (Parvathani et al., 2003). In the APPS1 mouse model of AD, Martin and coworkers observed a prominent expression of P2X7 mRNA in the CA3 region of the hippocampus along with an increased expression in the cortex and hippocampus compared to WT mice. P2X7 expression in microglia and astrocytes was also confirmed in this mouse model (Martin et al., 2019). More recently, Di Lauro and colleagues showed that P2X7 expression was increased in hippocampus necropsies of AD patients at mRNA and protein levels (Di Lauro et al., 2022).

Amyloid- β peptides found in the senile plaques of patients with AD derived from the cleavage of the amyloid precursor protein (APP) by β - and γ -secretases. Proteolytic processing of APP by α -secretase leads to the release of the soluble fragment of APP, sAPP α , which possesses neuroprotective properties. Using human and mouse neuroblastoma and primary glial cells, Delarasse showed that brief stimulation of P2X7 with ATP or BzATP triggers APP shedding by α -secretase, leading to an increase of sAPP α and a decrease of A β peptides levels (Delarasse et al., 2011). On the opposite, Léon-Otegui and colleagues demonstrated that α -secretase activity was reduced in Neuro-2a cells after prolonged stimulation of P2X7 by BzATP which resulted in the production of A β peptides (Leon-Otegui et al., 2011). In the J20 amyloid mouse model, a decrease of hippocampal amyloid plaques was observed after P2X7 inhibition with the antagonist Blue Brilliant G (BBG) and was correlated with a diminished GSK3 activity increasing α -secretase activity (Diaz-Hernandez et al., 2012). Also, lack of P2X7 in the amyloid model, APPS1, reduced amyloid load and the level of A β peptides (Martin et al., 2019). Thus, brief activation of P2X7 may activate α -secretase activity and release of sAPP α , while chronic activation of P2X7 may promote the production of A β peptides.

P2X7 plays a role in activating the NLRP3 inflammasome. Mice knockout for NLRP3 or caspase-1 show an overall attenuation of AD symptoms and an improvement in A β peptides elimination (Heneka et al., 2013). These results support the hypothesis that P2X7 contributes to neuroinflammation in AD by activating the NLRP3 inflammasome assembly. P2X7 was shown to be involved in microglia response to A β

peptide. Indeed, A β peptide-induced IL-1 β secretion in human microglia cell culture was abolished in presence of oxidized ATP (oATP), an inhibitor of P2X7 (Rampe et al., 2004). In accordance with these findings, microglia from P2X7-deficient mice were unable to release IL-1 β in response to A β peptide (Sanz et al., 2009). Moreover, increased IL-1 β production was observed in the brain of WT mice after intra-hippocampal injection of A β peptide but not in P2X7 KO mice (Sanz et al., 2009). However, in the chronic AD mouse model, APPS1, Martin et al. showed that P2X7 loss did not affect IL-1 β release in the brain (Martin et al., 2019). In fact, lack of P2X7 reduced levels of chemokines CCL3, CCL4 and CCL5 in the brain. This effect was associated with a pronounced decrease of the number of CD8+ T cells in the hippocampus and the choroid plexus (Martin et al., 2019).

P2X7 can also contribute to neuroinflammation spread in AD by increasing the production of ROS. Co-localization of the NADPH oxidase gp91phox subunit with P2X7-positive microglia was detected in APPS1 mice brains. In addition, higher neuronal damages were observed in P2X7-positive regions of the cerebral cortex suggesting that P2X7 could mediate neuronal damage via ROS production (Lee et al., 2011).

P2X7 seems to be involved in tauopathies other than AD and to contribute to neuroinflammation in these pathologies. For instance, overexpression of P2X7 was found in the cortex of patients affected by different tauopathies, namely frontotemporal lobar degeneration (FTLD), Pick's disease and progressive supranuclear palsy (Carvalho et al., 2021). Immunohistochemical analysis of brains from FTLD patients revealed that P2X7 expression is increased in astrocytes and microglia. Increased P2X7 mRNA and protein levels were also found in the hippocampus of the Thy-Tau22 tauopathy mouse model. In this model, P2X7 deletion reduced the expression of inflammatory markers known to be associated with Tau pathology in mice. Moreover, synaptic plasticity and memory impairments observed in this model were rescued in the absence of P2X7 (Carvalho et al., 2021). A recent study published by Di Lauro and colleagues, supports these findings. Using the P301S mouse model of tauopathy, they found that P2X7 expression was increased in the hippocampus of these mice at mRNA and protein levels.

The cognitive impairment was reversed after treatment with the P2X7 inhibitor, GSK 1482160 A. This effect was associated with an increase of microglia phagocytosis capacities and a reduced IL-1 β production. Interestingly, tau phosphorylation was decreased after P2X7 blockade. This was linked with an inhibition of GSK3 activity similarly observed in J20 mice (Di Lauro et al., 2022; Diaz-Hernandez et al., 2012). Interestingly, it has been also shown that P2X7 inhibition in P301S mice with GSK148260, decreased Tau accumulation and ameliorated memory impairments (Ruan et al., 2020). However, the beneficial effects were linked to a reduced secretion of Tau-containing exosomes with no effect on microglia activation (Ruan et al., 2020).

Altogether, these results indicate that targeting P2X7 represents a promising therapy in AD and other tauopathies. P2X7 blockade prevents the deterioration of AD cognitive features by impairing the release of pro-inflammatory factors and the recruitment of immune cells hence limiting brain neuroinflammation. In addition to this anti-inflammatory effect, targeting P2X7 would also enable the decrease of AD specific lesions: amyloid plaques and hyperphosphorylation of Tau (Fig. 3).

5.2. Huntington's disease

HD is an inherited neurodegenerative disorder caused by the autosomal dominant mutation of the *IT15* gene coding for Huntingtin HTT. This mutation leads to an abnormal repetition of the CAG triplet leading to apolyglutamine stretch in the N-terminal part of mutated mHTT protein (Popoli et al., 2008). The most significant symptoms of HD are motor impairments, but patients also exhibit cognitive disorders. Motor alterations are characterized by involuntary choreic movements, and the development of bradykinesia and dystonia in the late stage, characterized by loss of voluntary movement coordination (Popoli et al., 2008).

5.2.1. The role of A_{2A}R in HD

Many cerebral regions are affected and show signs of neurodegeneration. The most important neuronal loss is present in the striatum. The striato-pallidal neurons of the indirect motor pathway which strongly express A_{2A}R appear to be the most targeted by this degeneration (Schiffmann and Vanderhaeghen, 1993). The preferential expression of A_{2A}R in the early affected neurons was an argument to understand the role of the receptor in HD. Reinforcing the presumable role of A_{2A}R in HD, a genetic association between the genetic polymorphism of the *adora2a* gene and the age of development of HD was reported (Dhaenens et al., 2009).

Various studies have demonstrated that the A_{2A}R mRNA and protein levels was strongly and early decreased in the striatum of patients as well as in animal models of HD (Bauer et al., 2005; Glass et al., 2000). This alteration of the A_{2A}R expression is induced by alterations of the transcription processes or DNA methylation which are directly caused by the mHTT (Chiang et al., 2005; Villar-Menéndez et al., 2013). However, other studies reported an increase of the A_{2A}R-mediated signaling in striatal cells expressing mutated huntingtin supporting a complex functional interaction between mHTT and A_{2A}R, which remains unsolved (Tarditi et al., 2006; Varani et al., 2001). Altogether, these results suggest that the dysregulations of the A_{2A}R is associated with HD. In that way, numerous studies tried to address the role of A_{2A}R in HD pathophysiology.

The heterogeneous results of these studies highlight the complexity of the underlying mechanisms. The effects induced by pharmacological treatments in the study of the A_{2A}R role is largely dependent on the type of pharmacological compounds, the model of HD used, and the stage of the disease studied. Indeed, some studies demonstrate a beneficial effect of the use of A_{2A}R agonists, particularly in the R6/2 transgenic mouse model, expressing exon 1 of the human HD with around 150 CAG repeats, which are characterized by a decrease in accumulation of mHTT and improved motor activity (Blum et al., 2018; Cepeda et al., 2010; Chiang et al., 2009; Chou et al., 2005; Huang et al., 2011; Martire et al., 2007, 2013). On the other hand, in the same HD model, other studies

have also demonstrated the interest of using A_{2A}R antagonists allowing a reduction of the glutamate outflow and the NMDAR-induced toxicity (Domenici et al., 2007; Gianfriddo et al., 2004), factors actively involved in the neurodegeneration of striatal neurons. However, these effects seem to be observed only at early stages of the disease (Domenici et al., 2019; Martire et al., 2010). Other studies have reinforced the interest of the use of A_{2A}R blockade by the improvement of memory deficits associated with the pathology (Li et al., 2015; Tyebji et al., 2015). These results suggest the importance of A_{2A}R blockade in reversing, at least limiting, the characteristic dysfunctions and memory deficits that define this disease, although its impact on motor alterations remains poorly understood.

Moreover, other studies demonstrate contrary results during global knock-out of A_{2A}R in a 3-NP model, characterized by the systemic administration of the mitochondrial toxin 3-nitropropionic acid (3-NP) making it possible to mimic the anatomical deficits and behavioral aspects of HD (Fink et al., 2004; Huang et al., 2006). Indeed, these studies show that KO- A_{2A}R could have an exacerbating (Huang et al., 2006) or, conversely, protective (Fink et al., 2004) effect on neurological deficits and striatal alterations induced by the toxin. In contrast, a selective neuronal KO-A_{2A}R demonstrated an absence of impact on the pathology within this model, making it possible to highlight the role of A_{2A}R in non-neuronal cells. Reinforcing this hypothesis, a selective inactivation of A_{2A}R in bone marrow-derived cells (BMDCs) would have reduced the striatal damage observed in the 3-NP model (Huang et al., 2006). In that way, it has been demonstrated that in the R6/2 model, astrocytes could present altered glutamatergic signaling (Jiang et al., 2016). Interestingly, it is known that A_{2A}R deregulation induces modifications of astrocyte functions such as the reuptake of glutamate, which could thus participate in the excitotoxicity phenomenon which is characteristic of HD (Matos et al., 2012a, 2012b, 2013), thus consolidating the hypothesis of the involvement of A_{2A}R in glial cells although the field is under-explored.

In summary, although the modulation of A_{2A}R in the context of HD could be an interesting therapeutic avenue, in particular using antagonists, it would seem that the underlying mechanisms are still misunderstood, and it would require a greater exploration of the role of A_{2A}R within the different cells of the CNS on the development of characteristic lesions and associated motor and cognitive dysfunctions.

5.2.2. P2X4 role in HD

To our knowledge, no work established a link between P2X4 and HD pathophysiology.

5.2.3. P2X7 role in HD

The role of P2X7 in Huntington disease has not been fully investigated and little is known about the involvement of this receptor in this disease. In two mice models of Huntington disease Tet/HD94 and R6/1, increased P2X7 mRNA levels were detected in the cortex whereas increased protein levels of P2X7 were found only in the striatum specifically on synaptic terminals (Diaz-Hernandez et al., 2009). Additionally, calcium influx induced following BzATP stimulation (10 μ M of BzATP) was altered in primary cultures of cortical neurons expressing mutated Htt along with an increased vulnerability to BzATP-induced death compared to WT neurons. These detrimental effects were prevented by BBG suggesting a potential P2X7 involvement in neuronal death during HD (Diaz-Hernandez et al., 2009). Furthermore, treatment of R6/1 mice with the P2X7 antagonist BBG for 4 weeks attenuated the motor coordination deficit and neuronal loss without any effect on microgliosis or astrocytosis (Diaz-Hernandez et al., 2009). P2X7 appears to play a specific role in Huntington disease, however further studies are required to fully understand the role of P2X7 in in this disease.

5.3. Parkinson's disease

PD is the second most common neurodegenerative disease after AD.

The neuropathological hallmark of the PD is the degeneration of the nigrostriatal dopaminergic neurons of the *substantia nigra pars compacta* (SNc), mainly induced by an abnormal accumulation of alpha-synuclein protein aggregates known as Lewy bodies, (Kalia and Lang, 2015; Weintraub et al., 2022). This neurodegeneration leads to a dopaminergic depletion within the striatum leading to an alteration of motor activity regulation. Indeed, dopaminergic depletion causes a decrease of activation of D₁R and D₂R dopaminergic receptors of GABAergic neurons present in the striatum and thus leads to a decrease in activation of the direct motor pathway and an increase in activation of the indirect motor pathway. Together, these dysfunctions cause an inhibition of thalamo-cortical projections that normally regulates motor cortex activity. The consequences of the neural circuit alteration between striatum and motor cortex are the development of motor disorders characterized by bradykinesia, muscle rigidity, tremors, and postural instability.

To counter the development of these symptoms, the main treatment in the case of PD is dopamine supplementation with the dopamine precursor, L-dopa (Olanow et al., 2009). Although this treatment remains the most effective, taking it over the long-term induces motor fluctuations such as the appearance of involuntary movements like dyskinesia. The limitation of L-dopa treatment demonstrates the importance of understanding the underlying mechanisms induced in order to find alternative therapeutic pathways-

5.3.1. The role of A_{2A}R in PD

It has been shown that GABAergic neurons in the striatum strongly experience A_{2A}R which can heterodimerize with the D₂ receptors of the indirect motor pathway (Fuxe et al., 2010). During this heterodimerization, the A_{2A}R will have an inhibitory activity on the affinity and the signaling of the D₂ receptors, thus reinforcing the effects induced by the dopaminergic depletion in the striatum (Ferré et al., 1997). These results were validated using A_{2A}R antagonists which exhibited beneficial effects, in a dose-dependent manner, within numerous models of PD such as the 6-Hydroxydopamine (6-OHDA) mice model, characterized by unilateral intracerebral infusion of the dopaminergic neurotoxin 6-hydroxydopamine, and the MPTP model, induced by the treatment with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Authors of these studies observed a decrease in neuronal death and α-synuclein aggregation as well as a decrease in motor alterations such as bradykinesia (Grondin et al., 1999; Hodgson et al., 2010; Pinna et al., 2007, 2010, 2014; Smith et al., 2014). Interestingly, the blocking of A_{2A}R by an antagonist, when coupled with the L-dopa treatment, improved the quality and duration of the beneficial effects of L-dopa with an absence of the onset secondary symptoms onset induced by the long-term use (Kanda et al., 2000; Pinna, 2014; Rose et al., 2007). These promising results of the therapeutic targeting of A_{2A}R, in addition to the dopamine supplementation, have enabled the implementation of clinical trials (Kanda and Uchida, 2014) and the commercialization of the A_{2A}R antagonist istradefylline, (Dungo and Deeks, 2013). Together, these results suggest a primordial involvement of A_{2A}R in the development of the pathology and the associated motor symptoms associated, highlighting the importance of understanding the involved cellular mechanisms.

Although the role of neuronal A_{2A}R on dopaminergic signaling has been proved, other studies have demonstrated its involvement in the modulation of glutamatergic signaling which appears altered in the context of PD and would thus participate in the development of pathology (Moraes et al., 2021). Blocking A_{2A}R would limit the hyperphosphorylation of AMPA and NMDA receptors in striatal neurons and therefore counteract the alteration of glutamatergic signaling (Economou et al., 2004; Xiao et al., 2006). Although the role of A_{2A}R in other cells of the striatum is still misunderstood, a study demonstrated that the selective inactivation of A_{2A}R in neurons abolished the protective effects of the A_{2A}R antagonist on motricity but not the processes of neurotoxicity induced by the neurotoxin MPTP. This study highlighted different cellular mechanisms from A_{2A}R where the neuronal

A_{2A}R would modulate the processes related to motor activity while the glial A_{2A}R would modulate the processes of neuroinflammation in the context of PD (Yu et al., 2008a, 2008b). This hypothesis was reinforced recently by the demonstration of the involvement of A_{2A}R activation in the activation of pro-inflammatory microglial processes. Indeed, CD73 ectonucleotidase-mediated adenosine level limitation counteracted microglial inflammation and increased dopaminergic neurons viability in the MPTP model (Meng et al., 2019).

These results demonstrate the involvement of A_{2A}R in the development of PD but also highlight the complexity of the cellular mechanisms induced. The targeting of A_{2A}R seems to be a promising therapeutic route allowing a real improvement of symptoms and quality of life of patients with PD. On the other hand, in order to improve the beneficial effects of its targeting, it remains nevertheless necessary to precisely identify the role of A_{2A}R within the different cell types (Fig. 4).

5.3.2. The role of P2X4 in PD

Previous studies have proposed a role of P2X4 in PD (Khoja et al., 2016; Ma et al., 2020; Zhang et al., 2021; Wang et al., 2022). Using 6-OHDA rat model of PD, the upregulation of P2X4 in the SN has been observed and was linked with the acceleration of microglia activation during PD progression (Ma et al., 2020; Wang et al., 2022). When blocking pharmacologically P2X4 using 5-BDBD, an increased number of TH-positive neurons in the SNc of 6-OHDA rats has been observed (Wang et al., 2022). Among the molecular mechanisms proposed, P2X4 may modulate the production of interleukin factors such as IL-6, well-known for inducing cell damage on dopaminergic (DA) neurons (Ma et al., 2020). Moreover, when injecting a lentivirus to overexpress P2X4 in the SN of 6-OHDA rats, degeneration of DA neurons accompanied by a neuroinflammatory response has been observed. At the behavioral level, P2X4 overexpression aggravated PD symptoms (Ma et al., 2020).

The signaling pathways mediated via P2X4 in PD were covered by a few studies. Some of them found using P2X4KO mice an altered density of pre- and post-synaptic markers in the dorsal and ventral striatum. Moreover, an impairment in the dopaminergic pathways such as DARPP-32 have been found in the dorsal striatum when blocking P2X4 in the SN of 6-OHDA mice. At the behavioral level, P2X4 attenuated L-DOPA induced dyskinesia while potentiating its activity with ivermectin enhance motor signs (Khoja et al., 2016). Controversially, the administration of ivermectin was also inducing L-DOPA dyskinesia in P2X4KO mice which was time dependent. If ivermectin potentiates selectively P2X4 within P2X receptor family, ivermectin can also modulate other ligand-gated ion channels such as nicotinic or GABA_A receptors, suggesting that the effect of ivermectin in PD models is just partially mediated by P2X4 and thus, complex receptors networks may be involved in the L-DOPA responses (Khoja et al., 2016).

Another study observed that the overexpression of P2X4 in cells of 6-OHDA rats is able to increase NLRP3 inflammasome and caspase-1 protein expression, promoting cell apoptosis (Liu et al., 2018). Importantly, NLRP3 inflammasome mediates the aggregation of caspase-1, increasing levels of IL-1β and IL-18. Interestingly, levels of IL1β and IL18 were also elevated when overexpressing P2X4, confirming the activation of this pathway. These findings agreed with another study where a selective P2X4 antagonist and siRNAs were used to knock down P2X4 expression. Both strategies were able to inhibit the activation of the NLRP3 inflammasome and alleviated dopaminergic neurodegeneration and neuroinflammation (Wang et al., 2021). Thus, P2X4 mediating NLRP3 inflammasome activation may contribute to glial cell activation and dopaminergic neurodegeneration (Wang et al., 2021).

Furthermore, increasing work points at lysosomal dysfunction as a common feature in various neurodegenerative disorders such as HD, AD and PD (Zhang et al., 2021). The impairment of the autophagic pathways in which lysosomes are involved may be the result of a disrupted Ca²⁺ signaling. Indeed, Ca²⁺ signaling regulates various cellular functions that rely on lysosomes, including trafficking, autophagy, and neuronal differentiation (Kilpatrick, 2016). As previously described,

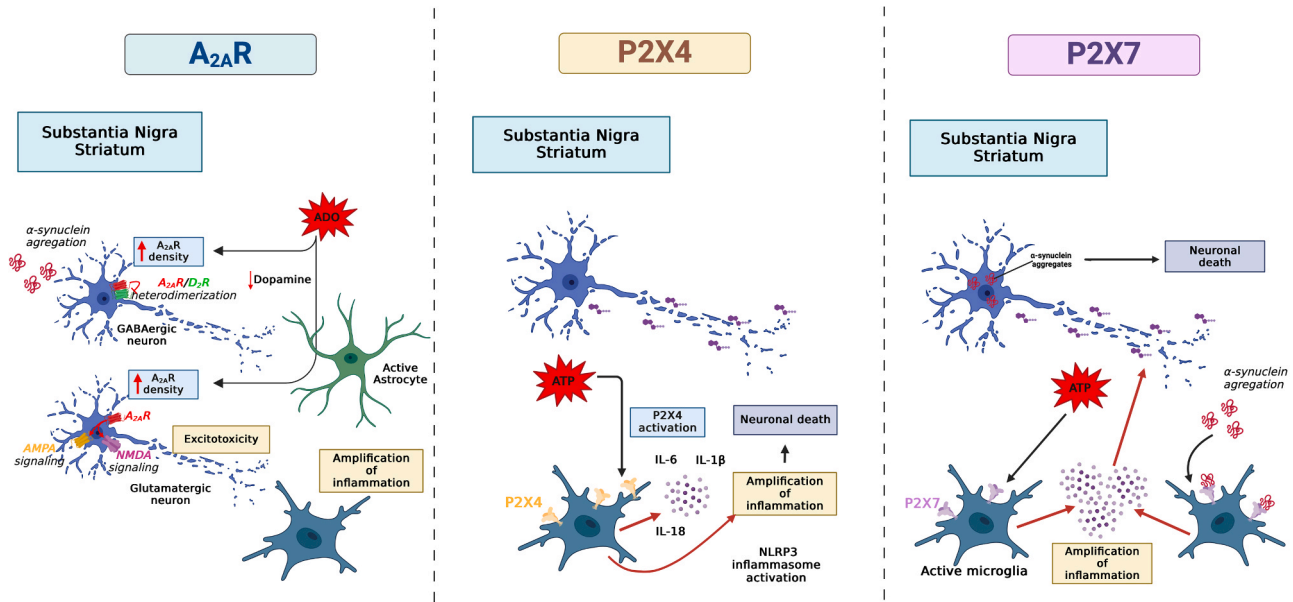


Fig. 4. Model of the roles of the purinergic receptors in PD. In the context of PD, an increase in A2AR density is observed in substantia nigra neurons. In GABAergic neurons, the latter heterodimerize with dopamine D2R receptors and inhibit their signaling, thus participating in the effects induced by extracellular dopamine depletion. In glutamatergic neurons, A2AR induces an increase in AMPAR and NMDA receptor signaling via their phosphorylation and thus causes excitotoxicity phenomena. Further, ATP released from damaged dopaminergic neurons and α -synuclein would bind to microglial P2X4 and P2X7. In PD, Microglial P2X4 has been related to the activation of the NLRP3 inflammasome pathway and to the release of proinflammatory IL-1 β , IL-6 and IL-18, promoting the amplification of the microglia reactivity, leading to the neuronal death. On the other hand, the activation of P2X7 in microglia induce the release of IL-1 β and reactive oxygen species enhancing neuronal death.

P2X4 receptor is mainly found in lysosomes, where it may allow the efflux of Ca^{2+} . The absence of P2X4 in 6-OHDA rats, affects autophagy by increasing the BDNF/TrkB signal pathway, leading to DA neuronal damage in the SNc. In patients with PD, downregulation of BDNF is frequently observed. On the other hand, blocking P2X4 activates autophagic pathways, thus promoting neuronal recovery (Zhang et al., 2021). Receptors able to modify Ca^{2+} levels in lysosomes such as P2X4 might contribute to the lysosomal dysfunction observed in both, animal models and PD patients (Zhang et al., 2021).

In summary, although few studies have focused on the role of P2X4 in the context of PD, blocking this receptor may help reduce DA degeneration. More research is needed to evaluate the potential of P2X4 antagonists as therapeutic options for fighting PD (Fig. 4).

5.3.3. P2X7 role in PD

Overexpression of P2X7 mRNA is found in the SN of PD (Parkinson's disease) patients (Durrenberger et al., 2012) and in the striatum of a rat model of PD (Oliveira-Giacomelli et al., 2019) along with active microglia in the striatum and the SN of PD patients (McGeer et al., 1988).

In vitro experiments have shown that α -synuclein is interacting with P2X7 on primary mice microglia culture. This interaction is leading to PI3K/AKT signaling pathway activation, NADPH oxidase activation and microglial activation resulting into dopaminergic neurons death (Jiang et al., 2015). Moreover, 6-OHDA-induced damage to dopamine-differentiated SH-SY5Y cells were attenuated by the antagonist BBG (Carmo et al., 2014).

In animal models of PD, several studies showed that P2X7 blockade using antagonists improved the behavioral symptoms of the disease suggesting P2X7 involvement in this pathology. In a rat model of Parkinson disease induced by 6-OHDA, blockade of P2X7 through systemic BBG administration improved motor and memory deficits, as evidenced by reduced contralateral rotations in the apomorphine induced rotation test and reduced short-term memory impairment in the Morris water maze test (Carmo et al., 2014). Similar effects were also observed when BBG was administered one week after 6-OHDA injection (Ferrazoli et al.,

2017) and after intracerebroventricular injection of BBG (Kumar et al., 2017) or the more selective antagonist A438079 (Carmo et al., 2014).

Furthermore, these beneficial effects were accompanied with a decrease of neuronal death and related to reduced microgliosis. Indeed, Carmo and coworkers observed a reduction of striatal dopamine loss and an attenuation of microgliosis and astrogliosis in the striatum of rat following BBG treatment (Carmo et al., 2014). In support of these findings, microglia activation was reduced in the substantia nigra of the 6-OHDA induced rat model of PD along with the restoration of Tyrosine Hydroxylase positive dopaminergic neurons in the striatum (Oliveira-Giacomelli et al., 2019). Likewise, in a rat model of PD induced by intranigral injection of LPS, BBG treatment prior LPS injection diminished microglia activation and prevented the loss of dopaminergic neurons of the substantia nigra (Wang et al., 2017). Increased release of IL-1 β in the substantia nigra related to microglia activation and dopaminergic neurons apoptosis (Koprach et al., 2008), thus P2X7-dependent IL-1 β release may be involved in this neurodegenerative process.

Overall, these results reinforce the hypothesis that microglial activation of P2X7 is involved in the worsening of PD as shown by *in vitro* and *in vivo* studies. P2X7 inhibition would reduce the microglia mediated neuronal cell death in the nervous system in PD (Fig. 4).

5.4. Multiple sclerosis

MS is the most common autoimmune disorder. Neuropathologically, it is characterized by overactivation of the immune system, significant gliosis, and demyelination along with immune cell infiltration into the CNS notably due to the blood-brain barrier (BBB) leakiness. These lesions ultimately lead to paralysis and cognitive impairments (Dobson et al., 2019).

5.4.1. The role of A2AR in MS

The A2AR receptor, present within the CNS as previously seen, is also expressed by immune cells such as T and B lymphocytes or macrophages. Interestingly, an abnormal A2AR upregulation has been observed in lymphocytes of MS patients compared to healthy subjects (Vincenzi,

2013). In addition, a PET study using a selective $A_{2A}R$ radioligand ([^{11}C]-TMSX) showed an increase of the receptor expression in the normal-appearing white matter (NAWM), a region strongly impacted in the MS disease and exhibiting strong demyelination and glial activation as well as a BBB impairment (Rissanen, 2013; Elliott, 2021). The authors demonstrated that this $A_{2A}R$ upregulation was correlated with a decrease in white matter (WM) volume in MS patients and an increase of the expanded disability status scale (EDSS) scores, allows the measure the pathology progression, thus highlighting the potential involvement of $A_{2A}R$ and adenosinergic signaling in its development.

One of the major pathophysiological hallmarks of MS is the alteration of the integrity of the BBB. Interestingly, an overexpression of the $A_{2A}R$ has been demonstrated within endothelial cells, which play important roles in the integrity of the BBB, particularly in regions exhibiting demyelination (Liu et al., 2018). Previous studies showed that $A_{2A}R$ modulate the integrity of the BBB, we can therefore hypothesize that its deregulation participates in the immune cell infiltration within the CNS in the context of MS (Kim et al., 2015).

Other works have completed these studies by highlighting the alteration of adenosine signaling and metabolism in MS patients, particularly through changes in the expression of CD73 ectonucleotidases and adenosine deaminases, enzymes directly involved in the adenosine metabolism (Kutryb-Zajac et al., 2022).

All these data support the therapeutic interest of targeting $A_{2A}R$ receptor in the context of MS. Experimental studies predominantly use the experimental autoimmune encephalomyelitis (EAE) model of MS which mimics lymphocyte infiltration, inflammation and demyelination observed in MS. Interestingly, this model exhibits an alteration of adenosine signaling characterized by an $A_{2A}R$ upregulation in lymphocytes, macrophages and microglia (Mills et al., 2012). Constitutive knockout of $A_{2A}R$ in this EAE model promoted an earlier and an exacerbation of the pathological development notably characterized by an enhanced T lymphocyte infiltration, demyelination, glial reactivity and inflammation as well as an increase of pro-inflammatory (IFN γ , IL17, IL6) and decrease of anti-inflammatory cytokines release (TGF- β , IL10) (Ingwersen et al., 2016).

On the other hand, these effects are seemingly more complex and would depend on other parameters, particularly the course of the

pathology itself. Indeed, the progression of the disease impacts the effects of $A_{2A}R$. Studies have shown that, once the disease is already ongoing, non-selective or selective $A_{2A}R$ antagonists (i.e. caffeine and SCH58261) reduced demyelination, proliferation and infiltration of immune cells but also glial reactivity as well as the release of pro-inflammatory cytokines such as IFN γ . Conversely, the use of the same molecules at MS onset rather exacerbates the pathological course (Chen et al., 2018). The use of selective agonists (i.e. CGS21680) would present opposite effects with a reduction of the pathology at early stages and, on the opposite, an exacerbation of its progression at more advanced stages (Ingwersen et al., 2016).

Furthermore, a study demonstrated that the role of $A_{2A}R$ in the development of MS could be dependent on its cellular expression. EAE $A_{2A}R$ constitutive knock-out mice, initially presenting an earlier and more severe development of the disease, transplanted with bone marrow cells from WT mice, exhibited slower development of motor symptoms (Mills et al., 2012). This study brings out the importance of $A_{2A}R$ expression by hematopoietic cells in MS development.

Together, these data demonstrate the major but complex role of $A_{2A}R$ in the development of MS, particularly in the EAE model, that remains to be further investigated. The role of $A_{2A}R$ seems to be dependent on several parameters such as the stage of the disease or its expression. A therapeutic window for A_{2A} -targeting molecules needs to be determined more precisely to consider their therapeutical use in MS patients (Fig. 5).

5.4.2. The role of P2X4 in MS

MS lesions are accompanied by microgliosis and neuroinflammation in many areas throughout the CNS such as optic nerve, spinal cord or cerebellum (Popescu et al., 2013; Schreiner et al., 2022). Interestingly, the optic nerve of MS patients showed an upregulated expression of P2X4 (Vázquez-Villoldo et al., 2014).

In the EAE model, increased P2X4 expression has been found in infiltrating macrophages in brain and spinal cord which was linked with the inflammatory process through EAE progression in rats (Guo and Schliesener, 2005). In addition, an overexpression of P2X4 has been found at the inflammatory foci and on activated microglia within the spinal cord of EAE rats. Although P2X4 activation is involved in MS

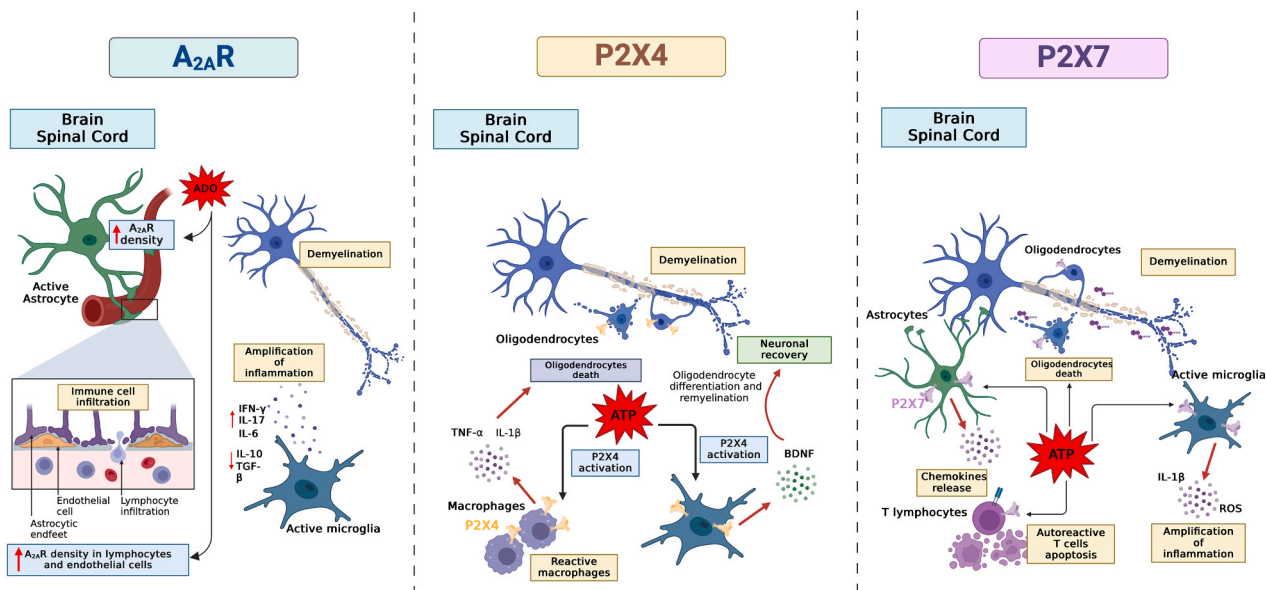


Fig. 5. Model of the roles of the purinergic receptors in Multiple Sclerosis. In MS, $A_{2A}R$ is increased in lymphocytes as well as endothelial cells, leading to impaired BBB integration and immune cell infiltration. This increase is also present within astrocytes which thus participate in the establishment of pro-inflammation. Moreover, microglial P2X4 in MS has been related to a beneficial effect in neuronal recovery by promoting oligodendrocyte differentiation and remyelination via BDNF released by microglia cells. Further, P2X7 activation on astrocytes and microglia during MS may contribute to the release of pro-inflammatory cytokines. ATP binding to P2X7 on oligodendrocytes induces their death promoting neuronal demyelination while it also would induce autoreactive T cells death.

progression, it seems to have an early beneficial role in the disease.

As previously mentioned, P2X4 activation in microglia is directly involved in the release of BDNF. This growth factor is well-known to promote oligodendrocyte differentiation and remyelination (Zabala et al., 2018). Using *ex vivo* organotypic cerebellar slices, Zabala and collaborators have revealed that P2X4 potentiation with the allosteric modulator ivermectin induced remyelination by promoting oligodendrocyte differentiation after lysolecithin-induced demyelination (Zabala et al., 2018). Thus, the blockade of P2X4 leads to a switch of microglia into a pro-inflammatory phenotype, inhibiting myelin phagocytosis and altering oligodendrocyte differentiation, a process extremely important in the regenerative response (Montilla et al., 2020). *In vivo*, ivermectin ameliorate clinical signs in mice with EAE, while both the P2X4KO mice and the pharmacological blockade of P2X4 with the antagonist TNP-ATP led to a worst prognosis (Zabala et al., 2018).

A potential lysosomal role of P2X4 may also contribute to MS pathogenesis. In EAE mice, ivermectin increases P2X4-mediated endo-lysosomal fusion in microglia, resulting in a higher phagocytic capacity which may be necessary for efficient remyelination (Zabala et al., 2018).

P2X4 in microglia is an active player in MS pathogenesis by promoting remyelination via BDNF release at early stages of the disease (Zabala et al., 2018). The previous findings may open the development of effective therapies targeting P2X4 for fighting MS (Fig. 5).

5.4.3. P2X7 role in MS

Post-mortem analysis of MS patients spinal cord revealed that P2X7 was co-localized with activated microglia and upregulated on astrocytes in the brain (Narcisse et al., 2005; Yiangou et al., 2006). Additional studies on brain samples from secondary progressive MS patients have shown increased P2X7 expression on astrocytes from the frontal cortex parenchyma (Amadio et al., 2017). Moreover, increased P2X7 expression is observed in normal appearing axonal tracts from MS patients before lesion formation implying that early P2X7 pathway deregulation is involved in the development of this disease (Matute et al., 2007).

Immunofluorescent staining analysis of cerebral cortex from EAE rats showed early increased expression by astrocytes and activated microglia (Grygorowicz et al., 2016; Grygorowicz and Strużyńska, 2019). Astrogliosis and microgliosis were reduced after BBG treatment along with inflammatory cytokines release in the brain. P2X7 inhibition also delayed EAE onset and improved neurological symptoms (Grygorowicz et al., 2016; Grygorowicz and Strużyńska, 2019). P2X7 involvement in MS pathology development was highlighted by *in vivo* studies showing that infusion of rat optic nerves with BzATP can trigger lesion like those observed in MS. Moreover, demyelination induced by EAE is reduced after BBG treatment and oligodendrocytes death can be induced by ATP and BzATP *in vitro* and *in vivo* (Matute et al., 2007). These results strengthen P2X7 crucial role in inflammatory process and oligodendrocytes loss during MS and support the use of P2X7 inhibitors as a therapy to improve MS symptoms.

However, *in vivo* experiments on P2X7 KO mice brought out conflicting results about the function of P2X7 during EAE. In a study published by Chen and Brosnan, EAE was exacerbated in P2X7KO mice compared to WT mice. Loss of P2X7 in these mice resulted in an exacerbation of inflammation and an overspread of destructive lesions in the CNS. In addition, mice brain and spinal cord analysis showed a decrease of apoptotic T cells number in these tissues. Loss of P2X7-dependent apoptosis of autoreactive T-cells is certainly responsible for the worsening of EAE (Chen and Brosnan, 2006). On the opposite, Sharp et al., noticed that EAE incidence was reduced in P2X7KO mice. This effect was linked with a decrease of astrocytes activation and axonal damages (Sharp et al., 2008). The differences between these two results can partially be explained by the transgenic mice used in these studies. Brosnan et al., used the P2X7KO mouse from Pfizer (Solle et al., 2001). This mouse is deficient for both isoforms P2X7(K), expressed in T cells, and P2X7(A), present in dendritic cells and macrophages. In contrast, Sharp et al., used the P2X7KO mouse from Glaxo-Smith-Kline (Chessell

et al., 2005) that still express the P2X7(K) isoform in T cells.

In MS, P2X7 would play a role in the immune response via P2X7 functions in microglia/macrophages and autoreactive T cells but also directly on demyelination via its expression by oligodendrocytes (Fig. 5).

5.5. Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS), also known as Charcot's or Lou Gehrig's disease, is a fatal neurodegenerative disease and the most common form of motor neuron diseases (MND). ALS is characterized by a gradual degeneration and death of motoneurons (MNs) in the spinal cord and the brain (lower and upper MNs respectively), leading to a progressive atrophy of the skeletal muscles and paralysis of the arms, legs and finally all members (Sebastiao et al., 2018).

Similarly, to other neurodegenerative diseases, ALS exhibits an alteration of purinergic signaling. Several studies have demonstrated an increase in ATP and adenosine levels in the cerebrospinal fluid of patients with ALS (Nukui et al., 2021; Yoshida et al., 1999). An increase in adenosine kinase and a decrease in adenosine deaminase, enzymes involved in adenosine metabolism, were also observed (Allen et al., 2019; Guo et al., 2020).

5.5.1. The role of A_{2A}R in ALS

ALS patients exhibit an abnormal increase in A_{2A}R in spinal cord cells but also in lymphocytic immune cells. Interestingly, A_{2A}R upregulation has been correlated with the Amyotrophic Lateral Sclerosis Functional Rating Scale- Revised (ALSFRS-R) scores demonstrating a direct link between receptor modulation and the development of pathology (Vincenzi et al., 2013).

This abnormal increase in A_{2A}R is notably found in the hippocampus and spinal cord in one of the most used mouse models of ALS, the SOD1^{G93A} mice, when the pathology is at an early stage. On the other hand, at late stages, and in contradiction with human post-mortem data, A_{2A}R levels in the spinal cord is strongly reduced in this murine model (Potenza et al., 2013). Therefore, A_{2A}R would present a dynamic expression that evolves during the pathology, at least in SOD1^{G93A} mice. These results could, however, provide a better understanding of the paradoxical data obtained by different experimental studies modulating A_{2A}R in the context of ALS.

Indeed, several studies show that the use of agonists and antagonists could both have beneficial effects in the context of ALS but via different mechanisms, with the presumable involvement of regional and cell-related mechanisms. The use of antagonist would delay the progression of the pathology with a reduction in the degeneration of MNs and a rescue of LTP in the hippocampus (Rei et al., 2020). In particular, the direct involvement of A_{2A}R overexpression in the alteration of hippocampal LTP/LTD processes has been demonstrated, which underline the beneficial use of receptor antagonists (Temido et al., 2018). Consistent with these data, A_{2A}R antagonists protected against excitotoxicity-induced MNs death (Mojsilovic-Petrovic et al., 2006). Glutamate excitotoxicity is one of the pathophysiological characteristics of ALS and it is interesting to note that A_{2A}R was previously shown involved in the regulation of glutamate and GABA levels though the regulation of their astrocytic reuptake (Matos et al., 2012a, 2012b).

It is known that the A_{2A}R can also modulate the activity and signaling of other receptors. One study particularly demonstrated that it can directly mediate signaling of the neurotrophin receptor TrkB, the receptor for BDNF. The use of A_{2A}R antagonist would limit the detrimental effect of TrkB signaling which causes vulnerability of MNs (Mojsilovic-Petrovic et al., 2005, 2006). Other studies, however, rather showed a benefit of using A_{2A}R agonists, which would delay the progression of the disease, by reducing the degeneration of MNs and preventing the mislocalization of TDP-43 in the cytoplasm, a characteristic alteration of ALS, via aberrant AMPK activity (Liu et al., 2015).

Although these data highlight the involvement of A_{2A}R in

modulating ALS progression, it appears, as for MS, that underlying mechanisms are complex and poorly understood. Many parameters could interfere and modify the effects of A_{2A}R. A_{2A}R may have a dual regulatory role with regards of the CNS and peripheral cells via respectively pro-inflammatory and immunosuppressive effects. This paradoxical effect is one explanation for the discrepancies observed in models (Fig. 6).

5.5.2. The role of P2X4 in ALS

Microgliosis is a typical feature of ALS disease in both patients and animal models (Bernaus et al., 2020). However, microglial activation depends on disease progression. At early stages of ALS, microglia exhibit an anti-inflammatory phenotype enriched with BDNF markers. However, as ALS progresses, microglia turns into a toxic deregulated phenotype, promoting MNs death (Volonté et al., 2019). Thus, microglia can exert dual roles, which are context dependent. In spinal cord of SOD1-G93A a mice model of ALS, P2X4 protein expression was first observed upregulated in microglia (D'Ambrosi et al., 2009). Interestingly, Bertin and colleagues have shown that P2X4 expression is restricted to MNs in ventral horn spinal cord of wild-type mice as well as during presymptomatic stages in SOD1^{G93A} mice whereas its expression increased in spinal microglia during ALS progression (Bertin et al., 2022). This finding may point out a time-dependent contribution of P2X4, so far unexplored.

Microglia-produced cytokines directly influence disease progression. Elevated systemic levels of inflammatory cytokines such as TNF- α , IL-6, IL-8 and IFN- β have been identified in ALS (Tortelli et al., 2020). P2X4 expression in microglia is required for effective production of IL-1 β and IL-6, indirectly via activation of P2X7 receptor (Volonté et al., 2019). Thus, P2X4 may contribute to ALS progression.

The main pathways involved in MN degeneration includes changes in Ca²⁺ homeostasis and AMPAR mediated excitotoxicity. However, some studies have shown that P2X4 mediated Ca²⁺ influx is able to induce cell protection in ALS. In MNs culture treated with ivermectin, Andries and collaborators reported that Ca²⁺ permeability promotes

MNs survival via P2X4 rather an indirect effect on AMPA receptors (Andries et al., 2007). Moreover, the protective effect seems to be dependent on ATP concentration. While low ATP doses protected MNs against excitotoxic stimulation, high concentrations of ATP were toxic. Remarkably, low ATP doses combined with ivermectin mimics the detrimental effect of high ATP concentrations, leading to cell death. *In vivo*, treating SOD1^{G93A} mice with ivermectin led to a 10 % increase of mice survival (Andries et al., 2007). Thus, these findings point out a direct beneficial involvement of P2X4 inducing cell protection which seems to be dependent on ATP concentration.

A strong increase of P2X4 expression was observed by immunohistochemistry in MNs before they degenerated in the ventral horn spinal cord from SOD1^{G93A} rats. P2X4 expression was detected as well in other degenerating neuronal populations, including noradrenergic neurons in the locus coeruleus, Purkinje cells in the cerebellum and serotonin containing neurons in the raphe nuclei (Casanovas et al., 2008).

Surprisingly, the same group showed later that the anti-P2X4 antibody used previously binds to misfolded SOD1G93A proteins in MNs but not in glial cells. Since the anti-P2X4 is directed against the C-terminal domain of P2X4, the authors revealed that the misrecognition of the mutated SOD1G93A protein by the anti-P2X4 antibody was due to a similarity of sequences between misfolded mutated SOD1 protein and the C-terminal of P2X4 (Hernández et al., 2010). Recently, Bertin and collaborators have shown that the mutated SOD1^{G93A} interacts with the adaptor protein AP2, acting as a negative competitor of the interaction between AP2 and P2X4, thus blocking receptor internalization. Overall, misfolded mutant SOD1 proteins in ALS altered the constitutive endocytosis of P2X4, leading to an increase of its presence at the cell surface (Bertin et al., 2022). This surface increase of P2X4 receptors also occurred in peripheral macrophages of SOD1^{G93A} mice even before the symptomatic stages. Using double transgenic SOD1 mice, either expressing P2X4 internalization-defective P2X4mCherryIN (P2X4KI) or deleting the P2X4 gene (SOD1-P2X4KO), it was shown that the surface increase or absence of P2X4, improved motor performance and survival of SOD1 mice, respectively (Bertin et al., 2022). This paradoxical result

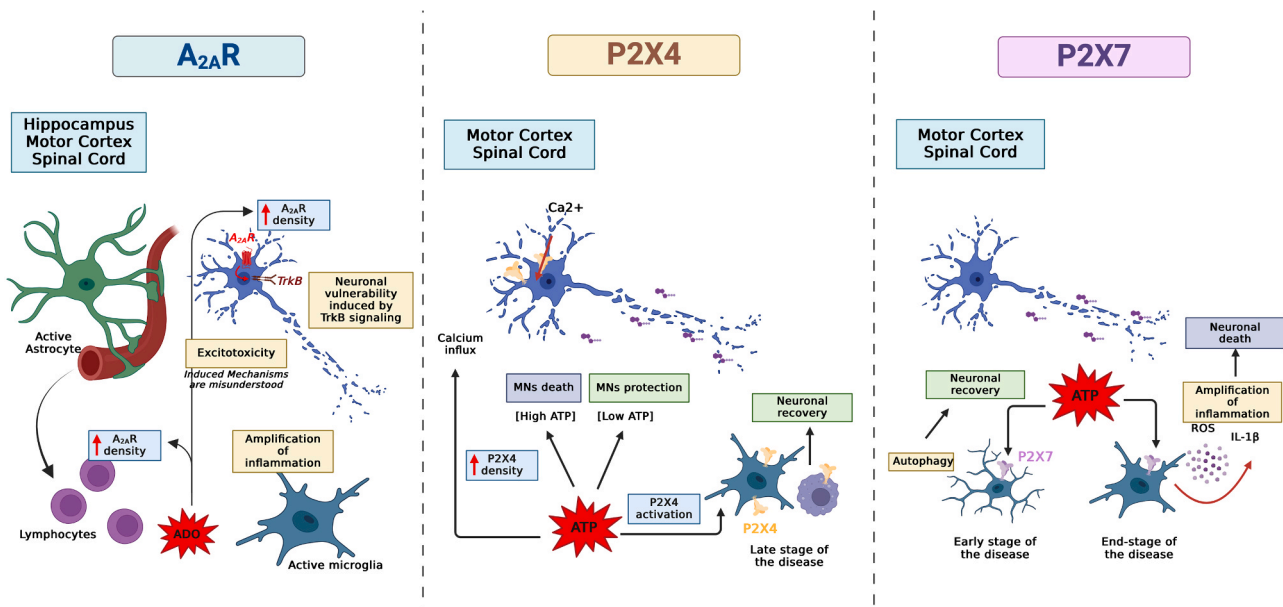


Fig. 6. Model of the roles of the purinergic receptors in Amyotrophic Lateral Sclerosis. In the context of ALS, an increase in the density of A_{2A}R has been observed in lymphocytes as well as neurons which then present a cellular vulnerability involving the TrkB receptor. Dual results have been observed when P2X4 receptors is activated by ATP in ALS, which may be dependent on ATP concentrations. In MNs, Low concentrations of ATP promotes MNs survival while higher concentrations promote MNs death due to a cytotoxicity cause by the increased influx of Ca²⁺ into these cells. On the other hand, the expression of P2X4 in immune cells such as microglia and macrophages seem to improve neuronal recovery at late disease stages. Finally, P2X7 activation in ALS by increased ATP concentration following MNs death would be beneficial at early stage of the disease by promoting autophagy and anti-inflammatory markers expression by microglia. At the end-stage of the disease, microglial P2X7 activation would be deleterious by inducing the release of pro-inflammatory cytokines.

highlights the duality of purinergic signaling, most likely due to cell- and time-dependent activation of P2X4 in ALS context (Fig. 6).

5.5.3. P2X7 role in ALS

Post-mortem analysis of ALS patients spinal cord revealed that P2X7 was upregulated in this tissue and co-localized with microglia/macrophage marker (Yiangou et al., 2006).

In vitro studies on SOD1^{G93A} primary microglia revealed that P2X7 activation by the agonist BzATP (10–100 μ M for 1 minute) amplifies the Rac1-NOX2 signaling pathway and enhances oxidative stress. P2X7 genetic deletion or inhibition with the antagonist BBG abrogated BzATP pro-inflammatory effects and diminished microglial ROS production (Apolloni et al., 2014). These results suggest that, in ALS, P2X7 activation can endow microglia with pro-inflammatory functions, contributing to the neuroinflammatory response. In addition to these findings, Fabrizio and colleagues observed that brief stimulation of SOD1^{G93A} microglia with ATP (3 mM for 15 minutes) or BzATP led to an increase of anti-inflammatory markers (CD163, ARG-1) expression and stimulates autophagy as observed with the increased expression of LC3-II. However, sustained activation of P2X7 with BzATP impaired autophagy in SOD1^{G93A} microglia (Fabrizio et al., 2017). It is hypothesized that, at the beginning of ALS, P2X7 activation in microglia is beneficial while at end-stage of the disease P2X7 becomes detrimental and promotes inflammation.

Several studies on the SOD1^{G93A} mouse model support this hypothesis. In this model, motor performances were diminished and loss of motoneurons were amplified in P2X7-deficient mice. This was accompanied with an increase of microgliosis and astrogliosis and a pronounced expression of pro-inflammatory markers, notably NOX2 and iNOS (Apolloni et al., 2013). On the contrary, P2X7 inhibition with BBG at the late pre-onset stage of the disease improved motor performances and delayed the onset of the disease. This was associated with an improvement of motoneurons survival, a reduction of microglial activation in the spinal cord, an upregulation of anti-inflammatory markers (BDNF, IL-10) and a down-regulation of pro-inflammatory markers (NF- κ B, COX-2, IL-1 β) (Apolloni et al., 2014). The discrepancy between these two results suggests that P2X7 could play different functions depending on the stage of the disease. In a recent study, the treatment of SOD1^{G93A} mice with the P2X7 inhibitor AXX71 at late pre-onset stage improved motor performances and muscular force but failed to maintain these effects after 50 days of treatment. At early-stage of the disease, AXX71 downregulated microglial pro-inflammatory markers expression in the spinal cord of SOD1^{G93A} mice however there was no impact on motoneurons survival, microgliosis and astrogliosis (Apolloni et al., 2021). Motoneuron cell body is surrounded by microglia in the CNS while the axon is surrounded by monocyte-derived macrophages in the peripheral nervous system and these cells were shown to have distinct functions in ALS (Boill e, 2022). In the SOD1^{G93A} mouse model, replacement of peripheral macrophages by macrophages with reduced neurotoxic properties slowed disease progression and also affected microglial activation (Chiot et al., 2020). In this line, P2X7 as well as P2X4 could play different functions in microglia and peripheral macrophages depending on the disease stages.

Recently, a study published by Bartlett et al., shed a new light on P2X7 role during ALS and its involvement in the prion-like propagation of SOD1. Transiently transfected NSC-34 neurons cells with SOD1^{G93A} were able to release aggregated SOD1^{G93A} upon ATP stimulation. Aggregated SOD1^{G93A} were then transmitted to neighbors' neuronal cells and induced endoplasmic reticulum stress, which can lead to cell death. Moreover, aggregated SOD1^{G93A} could activate EOC13 microglia cell line and induce the release of TNF- α (Bartlett et al., 2022).

In ALS, P2X7 appears to have protective functions at the early stage of the disease and to contribute to pathological mechanisms with the progression of the disease. In addition, the efficacy of central or peripheral inhibition of P2X7 differs. Consequently, identifying the specific role of P2X7 on the cell that express it would be of major interest in

ALS (Fig. 6).

6. Purinergic therapeutic strategies

Because the purinergic system is involved in many biological processes, therapeutic strategies have been developed in a wide range of diseases, including cardiovascular, neurological, urogenital, and respiratory conditions (Nakata et al., 2010). Several drugs targeting purinergic signaling in order to treat chronic inflammatory diseases have gone through clinical trial such as rheumatoid arthritis (Antonoli et al., 2019). Targeting the pro-inflammatory purinergic receptors may help to diminish the unbalanced release of cytokines and thus promoting tissue recovery (Fiebich et al., 2014).

Neurodegenerative diseases represent a heterogeneous group of pathologies. However, they share common elements: they can be considered as proteinopathies associated with chronic inflammation. As seen in this review, many studies have confirmed the involvement of purinergic receptors in neuroinflammatory process driving neurodegeneration, including AD, PD, MS, HD, or ALS (Apolloni et al., 2014). Hence, modulating the neuronal or inflammatory responses through the purinergic system may help to balance the neuroimmune crosstalk during neurodegenerative diseases, slowing the disease progression (Hodo et al., 2020; Liu et al., 2021).

Below we provide current findings on drug developed against neurodegenerative diseases targeting A_{2A}R, P2X4 and P2X7 receptors (Burnstock, 2017; Domercq and Matute, 2019; Pietrowski et al., 2021; Thawkar and Kaur, 2019).

6.1. Therapeutic targeting of A_{2A}R

The identification of A_{2A}R as a therapeutic target was first highlighted by the discovery of a major beneficial role of caffeine in slowing the development of various pathological contexts. Caffeine, a natural xanthine found in many everyday foods and beverages, is a non-selective A_{2A}R antagonist. Several epidemiological studies have shown that a reasonable daily consumption of caffeine, not exceeding 400 mg or 3–4 cups of coffee, improves cognitive functions (Haskell et al., 2005; James and Rogers, 2005; L pez-Cruz et al., 2018) and therefore made it possible to combat the memory deficits observed in the development of neurodegenerative diseases (Cellai et al., 2018; Flaten et al., 2014; Nehlig, 2016). In this sense, a phase III clinical trial has been set up in France (effect of Caffeine on Cognition in Alzheimer's Disease CAFCA). This study is based on the treatment of early-moderate AD patients by caffeine in a supervised manner over a period of 6 months to evaluate the impact on cognitive decline. In addition, it has been shown that the regular intake of caffeine helps to reduce chronic neuroinflammation which characterizes many neurodegenerative diseases. A reduction in pro-inflammatory cytokines TNF α and IL1 β , in particular via modulation of the NF κ B pathway, has thus been identified (Chen et al., 2008; Endesfelder et al., 2017; Kang et al., 2012; Lawrence, 2009; Ullah et al., 2015). Several experimental studies confirmed the beneficial effects of caffeine in the selective blocking of A_{2A}R in different animal models. Accordingly, A_{2A}R blockade has shown restoration of cognitive decline associated with AD lesions in experimental models even following short-term curative treatments, even at late pathological stages, when disease and memory decline are already presents. This is also the case in a model of AD-like tau pathology. Importantly, the selective A_{2A}R antagonist istradefylline has been the subject of a phase III clinical trial in Parkinson's disease patients and showed important property to reduce L-dopa side-effects improvement patients daily life (Hattori et al., 2020). These observations prompt to reposition this molecule in other pathologies notably dementia and rate tauopathies.

6.2. Pharmacological application of P2X4 in neurodegenerative diseases

P2X4 has been proposed as a therapeutic target mainly to modulate

microglia reactivity by either blocking its function particularly in chronic pain (Long et al., 2020), ischemia (He et al., 2022), and epilepsy (Ulmann et al., 2013), or potentiating its function in diseases such as spinal cord injury or MS (Montilla et al., 2020). However, because the P2X4 in neurons and glial cells have complex and opposing effects during disease progression, it is crucial to carefully consider both the nature of the molecule to be used and the timing of its administration relative to the disease stage.

Ivermectin is a positive allosteric modulator of P2X4 widely used in preclinical research to evaluate P2X4 contribution. Ivermectin potentiates selectively ATP-induced P2X4 responses by increasing ATP currents amplitude and/or by increasing and stabilizing P2X4 at the cell surface (Stokes, 2013; Silberberg et al., 2007). However, ivermectin does not specifically target P2X4 in the CNS, but also the GABA_A (Krussek and Zemkova, 1994) or the nicotinic acetylcholine receptor (Krause et al., 1998).

Ivermectin is an agonist of invertebrate glutamate-gated chloride channels used as an antiparasitic drug in human and veterinary medicine (Twum-Danso, 2003; Taticheff et al., 1994). This approved drug represents a fast and economical approach for drug reposition. Clinical trials using this compound have started in order to treat alcohol use disorders but effectiveness and safety of ivermectin to treat central disorders remain to be determined.

The key role of microglial P2X4 in different chronic pain models has accelerated the development of P2X4 antagonists as drug strategies to treat chronic pain. Among them, 5-BDBD seems to be a selective antagonist of P2X4 receptor (Coddou et al., 2019). Functionally, the use of 5-BDBD results in a rightwards shift in ATP dose-response curve (Stokes et al., 2017). In mice models of AD, the inhibition of P2X4 using this compound significantly improves neurological damages by reducing inflammation and microglia apoptosis (Thawkar and Kaur, 2019). Along with 5-BDBD, other compounds such as N-substituted phenoxazine, BX430 or carbamazepine derivatives have been identified as potent and selective allosteric antagonists of human P2X4. However, these compounds are less effective in mouse and rat P2X4 (Stokes et al., 2017). NP-1815-PX and NC-2600 demonstrated potent and specific inhibition against rodent and human P2X4. The phase I study of NC-2600 was completed, and despite a positive outcome on chronic pain and no serious side effects no further development was reported (Inoue, 2021).

Within this context, antibodies have a higher specificity compared to conventional small molecule drugs. Nowadays, development of camelid nanobodies modulating P2X4 function (positively or negatively) as showed for P2X7 (see below) represents the next-generation strategy to treat diseases where P2X4 is implicated (Bergmann et al., 2019).

Overall, despite the considerable efforts made to discover selective molecules targeting P2X4, only a limited number of drugs are available (Khoja et al., 2016). Further studies should be carried out to develop new and efficient drugs targeting P2X4. Drug-modulation of P2X4 may be a suitable target to act on immune responses, providing new avenues to fight neurodegenerative diseases.

6.3. Targeting P2X7 to reduce immune reactivity

Overall, P2X7 inhibition has shown promising results in different animal models of neurodegenerative diseases by decreasing the chronic immune reactivity, reducing the pathological lesions but also by improving cognitive deficits. The specificity of targeting P2X7 was validated using cells or mice deficient for P2X7. Several studies have used the P2X7 antagonist BBG to evaluate the effect of P2X7 inhibition in neurodegenerative diseases. Although these studies have provided important information on the beneficial effect of using P2X7 antagonists, this compound lacks specificity and possess several off-targets notably P2X1 and P2X4 (Young & Gorecki, 2018) and present a weak capacity to cross the BBB (Wang et al., 2004).

The development of antagonists for P2X7 is a subject of intensive research not only for neurodegenerative diseases but also for psychiatric

pathologies and several cancers (Savio et al., 2018). Many parameters must be considered: selectivity for P2X7, presence of off-targets, BBB permeability and residence time in the CNS. Moreover, the stage of the disease at which the drug would be administered should also be considered, as P2X7 has different functions depending on the cell type that expresses it and the pathophysiological environment as highlighted lately (Alves et al., 2024).

Recently, nanobodies directed against P2X7 have been developed and have shown encouraging results in mouse models of kidney inflammation and contact dermatitis (Danquah et al., 2016). Nanobodies are composed of the single variable immunoglobulin domains of heavy chain antibodies naturally found in alpacas. These nanobodies display several advantages over conventional antibodies and drugs: high specificity, increased tissue penetration due to their low molecular mass and capacity to modulate ion channel activity (Koch-Nolte et al., 2019). Furthermore, targeting of P2X7 on specific cell subsets could be achieved combining these nanobodies to nanobodies against cell-specific markers. Nanobodies open the way to an alternative strategy to inhibit P2X7 in neurodegenerative diseases.

7. Conclusion

Purinergic system is a complex and interactive system where ligands and receptors are involved in important biological processes and pathological processes. These complex cell- and time-dependent interactions among receptors result into beneficial and detrimental effects found among many neurodegenerative diseases such as HD, AD, PD, MS or ALS. The modulation of the purinergic receptor's may be useful to regulate immune responses occurring during neurodegeneration, serving as a promising future in the development of new drugs to treat neurodegenerative diseases.

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CRedit authorship contribution statement

Eric Boué-Grabot: Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization. **Cécile Delarasse Delarasse:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **David Blum:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Emilie Faivre:** Writing – review & editing, Writing – original draft. **Paul-Alexandre Dechelle-Marquet:** Writing – review & editing, Writing – original draft, Conceptualization. **Agathe Launay:** Writing – review & editing, Writing – original draft, Conceptualization. **Sara Carracedo:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests

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Data availability

No data was used for the research described in the article.

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