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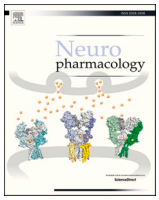

# P2 receptor-mediated signaling in the physiological and pathological brain: From development to aging and disease

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ABSTRACT

The purinergic pathway mediates both pro-inflammatory and anti-inflammatory responses, whereas the breakdown of adenosine triphosphate (ATP) is in a critical equilibrium. Under physiological conditions, extracellular ATP is maintained at a nanomolar concentration. Whether released into the medium following tissue damage, inflammation, or hypoxia, ATP is considered a clear indicator of cell damage and a marker of pathological conditions. In this overview, we provide an update on the participation of P2 receptor-mediated purinergic signaling in normal and pathological brain development, with special emphasis on neurodevelopmental psychiatric disorders. Since purinergic signaling is ubiquitous, it is not surprising that it plays a prominent role in developmental processes and pathological alterations. The main aim of this review is to conceptualize the time-dependent dynamic changes in the participation of different players in the purinome in shaping the normal and aberrant developmental patterns and diseases of the central nervous system over one's lifespan.

This article is part of the Special Issue on "Purinergic Signaling: 50 years".

## 1. Introduction

The focus of the present review is to update and summarize the literature on the participation of P2 receptor-mediated purinergic signaling in normal and pathological brain development, with a special emphasis on neurodevelopmental disorders (NDD) and their role in individuals through adulthood and aging and disease. Given the ubiquitous nature of the purinergic signaling, its involvement in developmental processes and pathological alterations is significant. Here, we will not provide a comprehensive overview because of the plethora of literature. Instead, we will attempt to conceptualize the dynamic changes in the expression of the purinome in shaping the normal and aberrant developmental patterns and diseases of the central nervous system (CNS) over one's lifespan.

## 2. Purinergic signaling during nervous system development

The "purinome" is a form of extracellular signaling mediated by purine nucleotides and nucleosides, mainly adenosine, adenosine triphosphate (ATP), and pyrimidines. Purines and pyrimidine nucleotides are released into the extracellular medium from living cells by several physiological mechanisms, such as exocytosis or diffusion through transporters and membrane channels (Burnstock, 2014).

Under physiological conditions, extracellular ATP is maintained at a nanomolar concentration. Whether released into the medium from lytic (e.g., stressed or apoptotic/necrotic cells) and non-lytic (e.g., pannexin-1 and connexins) routes, following tissue damage, inflammation, or hypoxia. Thus, elevated ATP is considered a "danger signal" for cell damage, implying that an abnormal and sustained elevation of extracellular ATP levels acts as an indicator of brain dysfunction (Cicko et al., 2018; Rodrigues et al., 2015). As ATP is suggested as a primitive danger signal, this suggests a common evolution of purinergic receptors with damage-associated molecular patterns. Indeed, purinergic signaling appears early in evolution and is already present in invertebrates (Burnstock and Verkhratsky, 2009). Therefore, it is unsurprising that purinergic receptors are abundantly expressed in different cell types and systems, including the CNS.

ATP and other nucleotides that are expressed early in the embryonic development of the nervous system mediate purinergic signaling pathways that modulate the long-term trophic effects necessary for embryonic development. Purinergic receptors play different roles as modulators or enhancers of the signal or direct functional switches of

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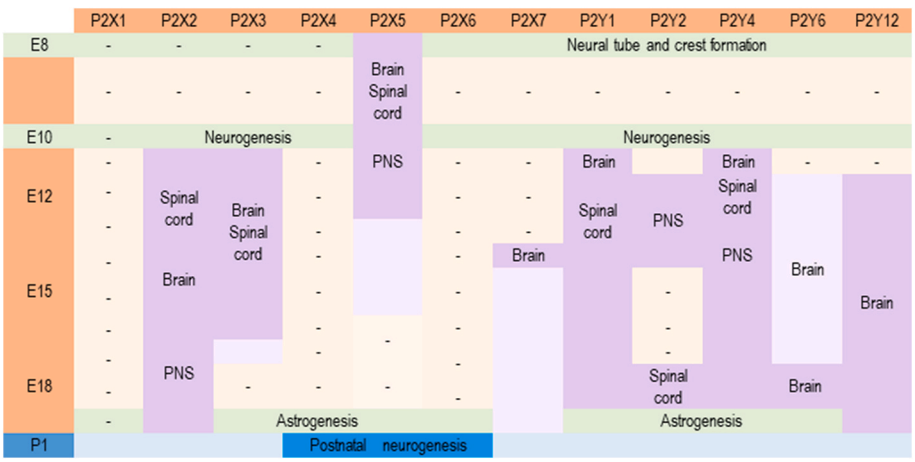


**Fig. 1. Approximate pattern of the expression of P2 receptors in development.** The purple color represents the time points at which the receptors appear in rodent embryonic days in the brain, spinal cord, or peripheral nervous system (PNS) and during the early stages of postnatal life (P). The light purple denotes the subtle expression or expected decrease of the expression of the receptor when indicated. The expression profile of P2X has been followed during perinatal brain development in the literature. While some P2X receptors may not play a role in development (P2X1 and P2X6 receptors) at first other subtypes might participate in different developmental processes depending on their first appearance in the embryo. P2X2 and P2X3 coexist in the PNS in E16.5 embryos. P2X3 appears early in the developing rat nervous system from E11 (Cheung and Burnstock, 2002). Although P2X3 seems to appear early at E11 in the development of rat brains, its expression declines in the following stages. On the other hand, P2X2 and P2X7 receptors were expressed from E14 onwards, while P2X4, P2X5, and P2X6 receptors were expressed only from P1 onwards (Cheung et al., 2005). P2X5 receptors have been found to appear early in the neural tube at E8 in the cortical plate and ventral horn of the spinal cord, after which they increase in expression to E13, peak at E9, and then continuously decrease until E17 (Guo et al., 2013). The P2X7 receptor is present in E15.5 (Tsao et al., 2013). In rat development, P2Y1 and P2Y4 receptors are strongly expressed from E11 to E18 during organogenesis and, on E12, become prominent in the neural tube. Although P2Y6 receptor expression was present as early as E11, expression was only barely detectable at E18. P2Y1 receptor expression occurs in the spinal cord, and P2Y2 and P2Y6 receptor subtypes gradually appear. P2Y2 receptors are also expressed in the dorsal root ganglia on E18 (Cheung et al., 2003).

purinergic pathways (Zimmermann, 2006). Therefore, the transient expression of some purinergic receptor subtypes and ectonucleotidases suggests that these nucleotides and nucleosides may affect developmental processes in a temporal and/or stage-specific manner. Moreover, ATP acts as a fast excitatory co-transmitter stored in all nerve types, both in the CNS and peripheral nervous system (PNS), and released from synaptic terminals, binding to many purinergic receptors. In the CNS, ATP and adenosine modulate communication between neuronal cells by mediating neuronal-glial communication (Verderio and Matteoli, 2011). This communication has been commonly associated with pathological conditions but is being increasingly recognized as associated with physiological conditions. For example, adenosine and ATP induce astrocyte proliferation (Neary et al., 2005) and modulate synaptic plasticity (Yamazaki and Fujii, 2015).

## 3. Brain development

The ubiquity of purinergic signaling in the nervous system suggests that nucleotides and nucleosides play multiple roles in neurogenesis and plastic remodeling during development. The brain entangles hierarchical neuronal and synaptic circuits, and proper excitation/inhibition dynamics are necessary for correct functioning. The process of brain development entails complex processes such as cellular programming or cell-to-cell communication, leading to the early neural induction of the CNS and PNS. Therefore, these can be enumerated mainly as the control of proliferation and the fate of neuronal cells, cell migration, maturation, synaptic pruning, apoptosis, maturation, neurite outgrowth, and synapse formation, as well as plasticity and network consolidation (Tierney and Nelson, 2009). Among these, cell survival is a highly regulated process essential for the correct function in the development and maintenance of the nervous system.

Mammalian embryo development is established from fertilization, cleavage, blastulation, and implantation through gastrulation, a pivotal early post-implantation event during which the three major germ layers (endoderm, ectoderm, and mesoderm) are specified with cellular and spatial diversity (Zhai et al., 2022). The mammalian embryo is formed by the embryonic tissue, which generates the embryo's body, and two extra-embryonic tissues, the trophectoderm and primitive endoderm, which generate the placenta and yolk sac, respectively. Stem cells are derived from three different tissues of the mouse embryo to form structures resembling embryos, emphasizing the self-organizing ability of stem cells (Sozen et al., 2018). Purinergic signaling is present in embryonic development since gastrulation but is prominent in mid-late embryogenesis, providing a potent contribution to organogenesis (Burnstock and Dale, 2015). Following gastrulation, the ectoderm gives rise to both epithelial cells and neurons. The inner cell mass of blastocysts rises into the neural tube, where progenitor cells differentiate to form the PNS and CNS, and these processes are largely regulated by purines and purinergic receptors (Oliveira et al., 2016).

Therefore, neurodevelopment is the process that shapes the nervous system from the earliest stages of embryonic development to adulthood. Dysfunctions in any of these processes and the processes mentioned above can result in malformations and intellectual disabilities. During nervous system development, progenitor cells and neural stem cells are converted into macroglial cells (astrocytes and oligodendrocytes) and neurons by symmetric and asymmetric divisions. Neurogenesis occurs first during embryogenesis, while glial cells develop mainly after birth. Neurogenesis occurs in two actively proliferating zones: the ventricular zone (VZ) and subventricular zone (SVZ) at both the prenatal and early postnatal stages. The VZ is a transient embryonic thin layer of tissue containing radial glial cells, progenitor cells responsible for producing all neuronal cell types, and specific glial lineages. It has been demonstrated that the role of nucleotides in regulating neurogenesis and neuronal survival is mediated by purinergic receptors (Arthur et al., 2006). Contributing to neocortex development in embryonic neural stem cells, ATP increases intracellular calcium release in radial glial cells, promoting neuronal proliferation (Weissman et al., 2004) and consequently contributes to neocortex development. Increased proliferation is believed to be triggered by ATP via the recruitment of quiescent cells into the cell cycle, increasing the number of radial glial cells (Barrack et al., 2014). There is increasing evidence of purinergic system pathways in both the embryonic and adult progenitor neural processes. For example, P2X receptors are expressed in rat neurospheres cultured in suspension and are mainly linked to neurogenesis and the induction of neuronal differentiation (Schwindt et al., 2011).

## 4. P2X expression and function in development

Purinergic P2X receptors are trimeric, ligand-operated channels. Each subunit comprises two transmembrane domains, intracellular C-

and N-termini, and a large ectodomain. Three ATP-binding sites, which contain highly conserved residues, are formed between the interface of the two subunits. The C-terminus is formed by a cysteine-rich region, which serves as an anchor to the cell membrane, and a 200-residue extended region that has been denominated as "cytoplasmic ballast" (McCarthy et al., 2019).

P2X receptors are exclusively activated by ATP and are sensitive to nanomolar concentrations (P2X1 and P2X3 receptors) and lower micromolar concentrations (P2X2 and P2X4 receptors). Exceptionally, P2X7 receptors are sensitive to much higher concentrations of ATP ($EC_{50}$ = 100 μM). As previously mentioned, extracellular ATP is an important signaling molecule that regulates several cellular functions that activate purinergic P2 receptors, which are expressed in the early embryonic stage and influence cellular differentiation, proliferation, and apoptosis (Burnstock and Ulrich, 2011; Cavaliere et al., 2015). P2X2 messenger ribonucleic acid (mRNA) and protein levels have been found to vary inversely with the change in ATP concentration in embryonic (E18) mouse prefrontal tissue (Kuang et al., 2022).

Recently, studies have been conducted on P2X receptors in *Xenopus laevis* embryos. The P2X2 receptor is expressed during gastrulation. The P2X4 receptor is expressed in the egg during segmentation, and its expression decreases during gastrulation. However, it is also present during organogenesis until adulthood. In contrast, the P2X6 receptor is present in egg segregation and gastrulation and then drops until adulthood. P2X5 receptor is present during neurulation. P2X7 receptor is the latest receptor present in late organogenesis (Blanchard et al., 2019). In addition, in the human placenta, there is evidence for functionally active P2X4 and P2X7 receptors in raising intracellular calcium (Roberts et al., 2006).

The expression profile of P2X was followed during perinatal brain development in rats. While some P2X receptors may not play a role in development (P2X1 and P2X6 receptors), other subtypes may participate in different developmental processes depending on their first appearance in the embryo (Cheung et al., 2005) (Fig. 1). However, in the mouse teratocarcinoma P19 cell line, an alternatively spliced form of the mouse P2X6 receptor gene was present in pluripotent undifferentiated P19 cells and was predominant compared to the full-length form during the whole course of neuronal differentiation of P19 cells. Alternative splicing has been suggested to regulate P2X6 receptor function during neuronal differentiation (Da Silva et al., 2007). Interestingly, in developing rat cochlea, mRNA and protein localization showed P2X1 expression from E16 to P6, but this expression was absent at later developmental stages (Nikolic et al., 2001). Recently, it was shown that P2X1 receptor-mediated calcium ion influx potentiates nerve growth factor (NGF)-induced neurite outgrowth in the rat neuroblastoma PC12 cell line, which is widely used as a cellular model for studies of neurotrophic action. The results obtained in this study suggest a possible relationship between the P2X1 receptor and neuroregeneration (Back et al., 2016).

The P2X3 receptor appears early in the developing rat nervous system from embryonic day 11 (E11) in the hindbrain neural tube and sensory ganglia. P2X2 and P2X3 receptors coexist in the nucleus tractus solitarius, dorsal root ganglion (DRG), nodose ganglion, and taste bud in the E16.5 embryo (Cheung and Burnstock, 2002). Although P2X3 appeared early at E11 in rat brain development, its expression declined in brain development and the early postnatal brainstems in the following stages. In contrast, P2X2 and P2X7 receptors were expressed from E14 onwards, whereas P2X4, P2X5, and P2X6 receptors were expressed only from P1 onwards. P2X3 might be implicated in neurite outgrowth while P2X7 receptors may be involved in programmed cell death during embryogenesis, and P2X4, P2X5, and P2X6 receptors might be involved in postnatal neurogenesis (Cheung et al., 2005).

During mouse embryo neurulation, P2X3 and P2X4 receptors are expressed, revealing a possible role in embryogenesis, while P2X1, P2X7, and P2X6 receptors are found in organogenesis (Massé and Dale, 2012).

P2X5 receptor expression increased specifically during phenotype transitions both in embryonic stem cells and neural progenitor cells (NPC) (Young et al., 2011), but it has been pointed out that its expression is limited to specific newborn neurons during early development (Guo et al., 2013). P2X5 receptors have been found to appear early in the neural tube at E8 in the cortical plate and ventral horn of the spinal cord, after which they increase in expression to E13, peak at E9, and then continuously decrease until E17. Specific expression in newborn neurons associates the receptor with neurogenesis and motor neuron development (Guo et al., 2013). The time, region, and cell type expression patterns of different P2 receptors show the involvement of ATP and its receptors in neuronal development and growth in organotypic slice co-cultures in the dopaminergic system comprising the ventral tegmental area/substantia nigra (VTA/SN) complex and the prefrontal cortex in three to five day old rats (Heine et al., 2007). GABAergic neurons derived from mouse embryonic stem cells elevate intracellular calcium predominantly via activation of P2X2 and P2X4 (Khaira et al., 2009).

Embryonic carcinoma cells are commonly used to study the proliferation and differentiation of cells during early embryogenesis. The importance of different receptors in cell fate has been demonstrated. In P19 embryonal carcinoma cells, P2X4 receptors or pharmacologically similar P2X-heteromultimers were found to be responsible for ATP and ATP analog-induced calcium transients. In neuronal differentiated cells, P2X2 and P2X2/P2X6 heteromeric receptors are the major mediators of elevation in intracellular free calcium concentration (Resende et al., 2008). During neuronal differentiation, P2X2 receptors are involved in neurogenesis, while the P2X7 receptor is involved in gliogenesis (Yuahasi et al., 2012). Furthermore, apoptosis occurs extensively during normal development as a vital process for the development of healthy neural precursor cells, differentiated postmitotic neurons, and glial cell populations. Multiple receptors are involved in this role, such as P2X4, P2X7, P2Y2, and P2Y6 (Förster and Reiser, 2015; Leeson et al., 2018; Solini et al., 2007; Xu et al., 2016).

The expression of P2X2-7 receptor subunits has been detected in differentiated neurospheres (Trujillo et al., 2012). Interestingly, a substantial increase in P2X2 and P2X6 receptors occurs upon the enrichment of neurons following neurosphere differentiation *in vitro* (Schwindt et al., 2011). P2X2 receptors undergo a significant decrease in expression when NPCs differentiate into neurons. P2X4 receptor expression decreases when embryonic stem cells differentiate into NPCs but recovers when NPCs differentiate into neurons, indicating its importance in neuronal fate determination (Young et al., 2011). Ongoing neuronal differentiation is accompanied by the downregulation of P2X4 and P2X7 receptor expression in rat telencephalon neurospheres (Oliveira et al., 2015). In human embryonic stem cells, embryoid bodies, and human embryonic stem cell-derived oligodendrocyte progenitor cells, all subtypes of P2X are present except for P2X6 (Kashfi et al., 2017).

P2 receptors are frequently downregulated during the postnatal period, suggesting that the purinergic system has a transient developmental role. It has been reported that the downregulation of purinergic signaling during neurogenesis and early development prevents the uncontrolled growth of progenitor cells and establishes a suitable environment for neuronal differentiation mediated by ectonucleotidases (del Puerto et al., 2013). These data might indicate that the regulation of purinergic signaling can modulate the process of neuronal differentiation, and after that, it might be accompanied by a rapid loss of purinergic signaling. During the development of the lateral ventricular choroid plexus of the rat, all known mammalian nucleotide receptor subtypes, except for the P2X7 receptor (detected from E18), were identified as early as E15. In addition, differential mRNA expression patterns were observed for the different receptors during development, and transient peaks for receptor proteins were detected immunohistochemically in the choroidal epithelium from early in development (E15 or E18), suggesting a specific role during different stages of development of cerebrospinal fluid secretion and, therefore, for the rapid expansion of the

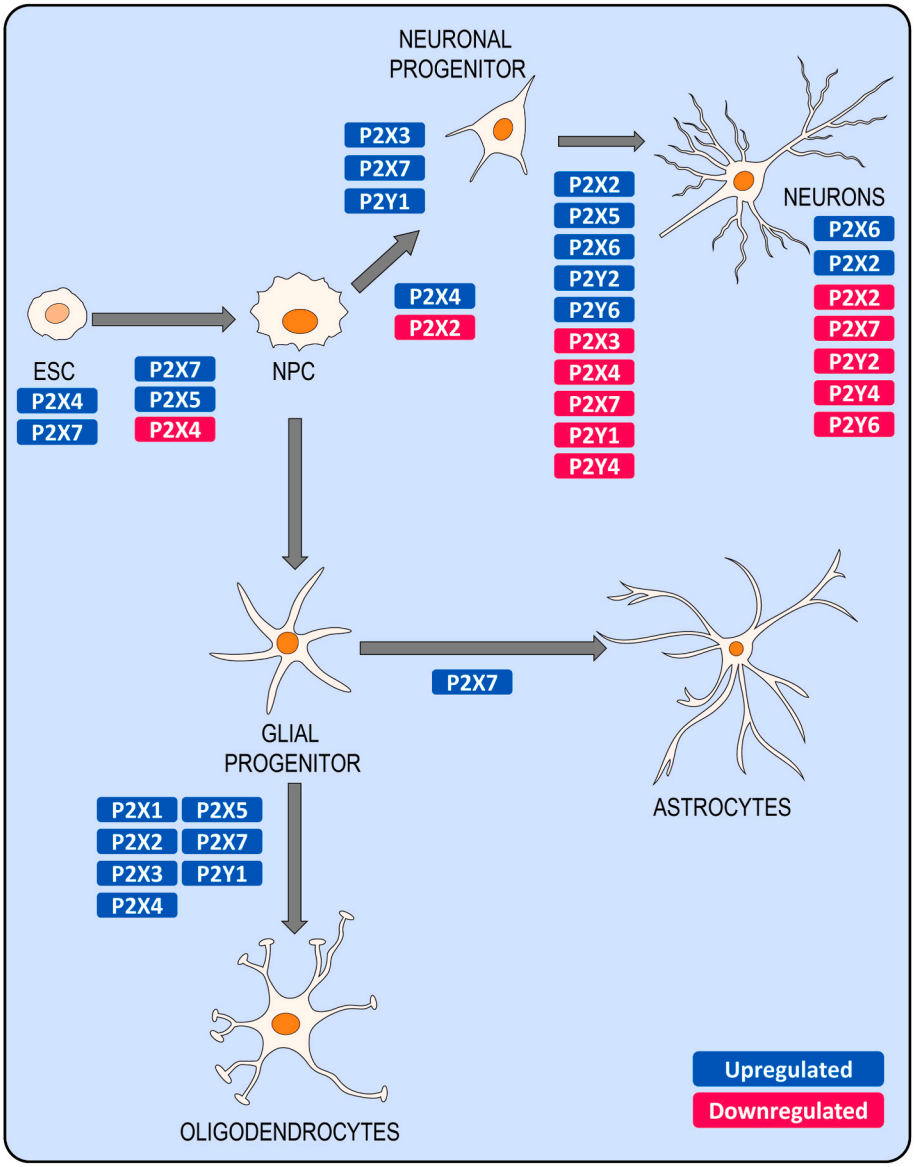


**Fig. 2. Activity of P2 receptors through neuronal and astroglia differentiation.** In embryonic stem cells (ESC), P2X4 and P2X7R expression and activity are upregulated (Glaser et al., 2014; Young et al., 2011). Upon differentiation to neural progenitor cell (NPC), the presence of P2X7 (Messemer et al., 2013) was observed, which is in contrast to P2X4, which needs to be suppressed. P2X5 receptor expression also increased specifically during phenotype transitions from ESC to NPC (Young et al., 2011). NPC gives rise to both neuronal and glial progenitors. P2X2 receptors underwent a significant decrease in expression when NPCs differentiated into neurons and were recovered when NPCs differentiated into neurons showing its importance in neuronal fate determination (Young et al., 2011). P2X3 has been involved in neurite outgrowth (Cheung et al., 2005), while P2X1 and P2X7 are associated with initial axon elongation and initial neuronal proliferation accompanied by a posterior downregulation (Oliveira et al., 2015). It has been pointed out that P2X5 expression is limited to specific newborn neurons during early development (Guo et al., 2013). In differentiated neuronal cells, a substantial increase in P2X2 and P2X6 receptors occurred upon enrichment of neurons following neurosphere differentiation *in vitro* (Schwindt et al., 2011). However, in another study, P2X2 receptors underwent a significant decrease in expression when NPCs differentiated into neurons (Young et al., 2011). *In vitro* differentiation of P19 murine embryonal carcinoma cells resulted in both increases of P2X2, P2X6, P2Y2, and P2Y6 and downregulation of P2X3, P2Y1, and P2Y4 receptors during neuronal differentiation (Resende et al., 2007). In addition, rat-derived embryonic NPCs showed decreased expression of P2X7, P2Y2, P2Y4, and P2Y6 receptors 14 days after the induction of neural differentiation (Oliveira et al., 2015). P2X7 was involved in gliogenesis (Yuahasi et al., 2012). In human embryonic stem cells, oligodendrocyte progenitor cells, all subtypes of P2X are present except for P2X6 (Kashfi et al., 2017). P2Y1 has been also involved in oligodendrocytes differentiation (Agresti et al., 2005; Lecca et al., 2021).

ventricles that occur in the embryo (Johansson et al., 2007).

The P2X7 receptor is sensitive to high concentrations of ATP, suggesting a specific role for this receptor under pathological conditions when cell loss or inflammation provides an ATP-rich extracellular milieu. However, the P2X7 receptor also performs several physiological functions in the CNS, including cell proliferation, cell growth, neurotransmitter release, and intercellular communication (Skaper et al., 2010; Sperlágh and Illes, 2014; Tewari and Seth, 2015). Moreover, the P2X7 receptor is expressed early in rats (Cheung et al., 2005) and in human induced pluripotent stem cell (hiPSC)-derived microglia-like cells, hiPSC-derived neuronal progenitors, and hiPSC-derived mature neuronal cells (Francistiová et al., 2022). Extracellular levels of ATP are strongly associated with the development of neuritic processes in cultured hippocampal neurons mediated by tissue-nonspecific alkaline phosphatase, which at the same time is functionally interrelated with the P2X7 receptor. Both are important for axonal development, showing different regulatory effects *in vitro* (Díez-Zaera et al., 2011). It has been hypothesized that the P2X7 receptor promotes initial proliferation, as its expression is higher during earlier *in vitro* days in rat telencephalon neurospheres while being downregulated during the 14 days in culture during neuronal differentiation (Oliveira et al., 2015). During development, P2X7 receptors appear to be involved in necrosis and apoptosis (Kanellopoulos and Delarasse, 2019), whereas other *in vitro* studies have demonstrated different regulatory effects on axonal growth and branching (Díaz-Hernandez et al., 2008). Extracellular ATP provokes avian retinal cholinergic neurons via the P2X7 receptor during normal development as a control of proper density (Anccasi et al., 2013).

Therefore, the P2X7 receptor may be involved in regulating the uncontrolled differentiation and migration of cells during neurogenesis. Finally, it is hypothesized that the role of the P2X7 receptor in maintaining both neural stem and progenitor pools by inducing proliferation or apoptosis might depend mainly on the microenvironment (Oliveira et al., 2016). In mouse embryonic stem cells, the expression and activity of the P2X7 receptor are upregulated, maintaining and accelerating cell proliferation *in vitro*, whereas P2X7 receptor expression needs to be suppressed upon induction of neural differentiation (Glaser et al., 2014). In contrast, the P2X7 receptor is present in the embryonic rat brain (E15.5) in SVZ and VZ NPCs, and its activation induces neuronal differentiation *in vitro* (Tsao et al., 2013). In NPC cultures obtained from adult mouse brains, the P2X7 receptor was functional in both *in vitro* differentiation and *in vivo* maintenance of NPCs (Messemer et al., 2013).

Patch-clamp recordings in the subgranular zone (SGZ) of the rodent hippocampus showed P2X7 and P2Y1 receptor-mediated currents in the NPCs. This becomes more striking after pilocarpine-induced status epilepticus, when increased receptor immunoreactivity at NPCs was observed for both receptors, hypothesizing a complementary role for the receptors. P2Y1R may increase ATP-induced proliferation and ectopic migration of NPCs, while P2X7 receptor-mediated apoptosis probably counteracts the status epilepticus post-effects (Rozmer et al., 2017).

Therefore, P2 receptors might present different expression activity patterns to guide the proliferation and differentiation of neuronal cells (Fig. 2). Recently, a novel role of the P2X7 receptor in neuronal branching in the initial stages of development under physiological conditions has been demonstrated. Transient expression of the receptor during brain development affects dendrite branching and spine density (Mut-Arbona et al., 2023).

Postnatally, the immunoreactivities of P2X1, P2X4, and P2X7 receptors were demonstrated in primary cultured microglial cells from P3 rats, influencing the differentiation and maturation of amoeboid microglial cells (mainly via P2X1 and P2X4) and mediating extracellular ATP actions in different conditions, in resting microglial cells, but also in pathological conditions such as inflammation, injury, and degeneration disease (Xiang and Burnstock, 2005). It has been reported that the downregulation of purinergic signaling during neurogenesis and early development prevents the uncontrolled growth of progenitor cells and establishes a suitable environment for neuronal differentiation mediated by ectonucleotidases (Cavaliere et al., 2015). In adult neurogenesis, in neural progenitors from the adult dentate gyrus of the hippocampus, nucleotides activate cells in acute slices, and ATP induces an inward current, implying the expression of P2X receptors (Shukla et al., 2005). Similarly, P2X receptor-mediated inward currents were observed *in vitro* undifferentiated adult hippocampal progenitors (Hogg et al., 2004).

## 5. P2Y expression and function in development

The G protein-coupled metabotropic P2Y receptor subfamily contains eight subunits (P2Y1, 2, 4, 6, 11, 12, 13 and 14) activated by ATP and other nucleotides (adenosine diphosphate, uridine diphosphate (UDP), uridine triphosphate (UTP), or UDP-glucose). P2Y receptor-encoding mRNA or protein has been detected at different periods in the developing brain (Fig. 1). During rat development, P2Y1 and P2Y4 receptors are strongly expressed from E11 to E18 during organogenesis. Although P2Y6 receptor expression was present as early as E11, it was barely detectable at E18. However, on E12, P2Y1 and P2Y4 receptor expression were prominent in the neural tube. Interestingly, P2Y4 receptor expression was downregulated in the brainstem after birth, suggesting a specific role in prenatal brain development. In contrast, P2Y1 receptor expression occurs in the spinal cord, and the P2Y2 and P2Y6 receptor subtypes gradually appear. P2Y2 receptors are also expressed in the dorsal root ganglia on E18 and are specifically observed in spinal motor nerves, supporting the purinergic system's role in sensory systems and motor neuron development (Cheung et al., 2003).

P2Y purinergic receptors seem to coordinate with growth factor signaling during neurogenesis (epidermal growth factor (EGF)) in cultured adult murine neural stem cells (Grimm et al., 2010). Rat-derived embryonic NPCs showed decreased expression of P2X7, P2Y2, P2Y4, and P2Y6 receptors 14 days after the induction of neural differentiation (Oliveira et al., 2015). Moreover, cell proliferation is reduced in P2Y1-deficient neurospheres, even in the presence of EGF (Mishra et al., 2006). However, it remains unclear whether P2Y receptors work closely with NGF to result in neurite extension (Arthur et al., 2005). During the initial axonal elongation, P2Y1 receptor, in coordination with the P2X7 receptor, is now believed to be essential for proper axon elongation. P2Y1 receptor activity and expression are necessary for mouse primary hippocampal neurons during initial development but have no role once maturity is achieved (Zhang et al., 2019). *In vitro* differentiation of P19 murine embryonal carcinoma cells into neurons has been used to study purinergic receptors during development. Functional P2X4, P2X7, and P2Y1 receptors were detected with a posterior gene and protein increase in P2X2, P2X6, P2Y2, and P2Y6 and downregulation of P2X3, P2Y1, and P2Y4 receptors during neuronal differentiation (Resende et al., 2007).

P2Y1 receptors have been shown to be involved in regulating numerous functions of embryonic and adult neuronal stem cells (NSCs). P2Y1 subtype-specific antagonists have been suggested to induce the proliferation of SVZ radial glial cells, as shown in E16-17 rat embryo brain slices (Weissman et al., 2004). Purines have been shown to expand the VZ neural stem and progenitor cells, and purine receptor activation is required for proper cell density maintenance, which functions as a critical regulatory checkpoint. Therefore, progenitor cells are maintained by P2Y receptor antagonists *in vitro*, which suppress proliferation and permit differentiation into neurons and glia (Lin et al., 2007). Therefore, the result of the purinergic signaling will depend not only on the nucleotide and the receptor that is activated but also might vary depending on the cell type and other elements of the pathway signaling (Fig. 2).

The P2Y12 receptor is expressed in human microglia under physiological conditions throughout development and is implicated in neuroinflammatory diseases. An increase in microglia in the cerebellar molecular cell layer has been observed during development, but a significant decrease in microglial density in the cerebellar white matter between birth and early adulthood has also been observed. In general, P2Y12 has been detected in fetuses, newborns, children, adults, and elderly brains, and quantification of microglial cell numbers in the cerebellum and cortex has revealed a more or less stable P2Y12 positive microglia population postnatally (Mildner et al., 2017).

## 6. P2X in adult physiology: conserving developmental properties

Purinergic signaling regulates the proliferation, differentiation, and migration of neural stem cells and NPC in the adult brain in selected forebrain regions: the adult SVZ on the lateral ventricles or the subgranular layer of the dentate gyrus of the hippocampus (Götz and Huttner, 2005).

When several signals in the environment activate radial glia-like cells in the adult hippocampal neural stem of the SGZ, they proliferate and divide into intermediate neural progenitors. Then, they will subsequently differentiate into both neuroblasts that give rise to dentate granule cells or, to a lesser extent, astrocytes (Toda et al., 2019). ATP and purinergic receptors have been proposed as modulators of adult neurogenesis; however, only a few receptors play a prominent role in this process: P2X7, P2Y1, and P2Y13 receptors (Leeson et al., 2019; Stefani et al., 2018; Suyama et al., 2012). Recently, a deficiency in P2Y2 was found to negatively affect the proliferation of NPCs in the SGZ and SVZ, accompanied by impaired performance in the Y-maze and a higher latency in the hidden food test, suggesting a new role for the receptor in adult mouse neurogenesis and cognitive performance (Ali et al., 2021).

In both embryonic and adult neural progenitor cell niches, the P2X7 receptor is still present (Tang and Illes, 2017). It has been recently reported that the P2X7 receptor plays at least three separate roles in the adult hippocampus, influencing the hippocampal neurogenic niche depending on the extracellular ATP concentration. At low extracellular ATP levels, the P2X7 receptor mediates calcium transduction signals that regulate biological functions such as proliferation and differentiation in adult neurogenic niches. Contributing to damage repair in the adult brain, the P2X7 receptor inhibits the growth of neuroprogenitors at the expense of promoting differentiation into neurons and astrocytes. In the presence of inflammation, the high concentration of ATP, or in the opposite physiological conditions, in the absence of the nucleotide, the P2X7 receptor might elicit different responses, such as promoting cell death or phagocytosis, respectively (Leeson et al., 2019).

P2Y1 stimulation increased calcium wave propagation and

consequently provoked cell proliferation in neurospheres cultured from the adult mouse SVZ synergistically with mitogenic growth factors, enhancing adult neurogenesis (Mishra et al., 2006). Intracerebroventricular injection of a P2Y1 selective antagonist inhibited ATP-derived neurogenic proliferation in the SVZ (Suyama et al., 2012), whereas injection of the agonist into mouse cerebral ventricles increased the number of astrocytes in the brain parenchyma and proliferation of NSCs in neurogenic areas of the SVZ (Boccazzi et al., 2014). A recent fluorescent *in situ* hybridization study in young adult mice showed P2Y13 receptor mRNA expression only in microglia. Disruption of the receptors negatively impacts the structural complexity of microglia in the hippocampal SGZ, and interestingly, P2Y13-deficient mice present increased progenitor cell proliferation and new neuron formation in the same area. Therefore, P2Y13 receptors in microglia may participate in the homeostatic control of adult hippocampal neurogenesis by attenuating hippocampal neurogenesis (Stefani et al., 2018).

## 7. Exploring P2X receptors in pathology through a neurodevelopmental lens: insights from maternal immune activation (MIA) models from development to young adulthood

An insult during the prenatal or early life stages might be a predisposing factor for the development of NDD. These insults might compromise brain function by causing abnormal morphological alterations, neurotransmission, and connectivity (Adams-Chapman, 2009; Selemon and Zecevic, 2015). It has been pointed out that a prenatal infection during the first or second trimester of pregnancy due to a maternal bacterial or viral infection (e.g., maternal influenza infection) could be the principal cause of increased susceptibility to developing subsequent NDD such as autism or schizophrenia in the offspring post-puberty (Meyer et al., 2005; Shi et al., 2003; Solek et al., 2018). Indeed, it has been identified that the maternal immune-inflammatory response contributes to neurodevelopmental disruptions through the imbalance of the main maternal interleukins, such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNFα), IL-1β, and IL-17A (Bergdolt and Dunaevsky, 2019). A Mendelian randomization study found that IL-6 was associated with changes in brain structure, especially in the middle temporal gyrus, an area in the human brain that differentially expresses genes that are functionally enriched for biological processes in schizophrenia, autism spectrum disorder and epilepsy (Williams et al., 2022).

Consequently, several models subjected to MIA have been used to model autism and schizophrenia to understand the entire spectrum of these diseases. These models commonly consist of injecting pregnant rodents with an immunogen at different gestational days, such as polyinosinic:polycytidylic acid, usually abbreviated as poly(I:C) (PIC), influenza virus, and/or the bacterial endotoxin lipopolysaccharide (LPS) (Solek et al., 2018).

PIC is a synthetic analog of a viral double-stranded ribonucleic acid (RNA) that activates Toll-like receptors (TLR)-3, triggering an anti-viral immune response in the absence of the pathogen (Patterson, 2009). On the other hand, LPS, as a significant part of gram-negative bacteria's outer membrane, causes an anti-bacterial immune response by ligating TRL-4. The mechanism of action is different, and so are the effects on the offspring.

Depending on the time point of injection, it also affects several processes in brain development. For example, critical malformations during cortical development have been observed in the offspring of pregnant dams subjected to MIA, which show repetitive behavior and social deficits (Choi et al., 2016). Indeed, cortical patches in the primary somatosensory cortex have been identified as a prognostic factor of MIA-altered behaviors and the severity of behavioral disruption in offspring from dams injected with PIC at E12.5, but not E15.5 or E18.5 (Shin Yim et al., 2017).

*Schizophrenia* is now also regarded as an NDD since an insult at the prenatal or early life stage might become a possible predisposing factor to the disease. Schizophrenia is a chronic mental disorder with an estimated prevalence of 0.5%–1%, with a young adulthood onset characterized by an array of psychotic symptoms, deprivation of emotional responses, and cognitive impairments associated with substantial comorbidities such as anxiety, substance abuse, and depression, leading to a high incidence of suicide attempts. It is considered one of the leading causes of life-long disability among psychiatric disorders (Lewis and Gonzalez-Burgos, 2006). Multiple symptom ranges have been previously grouped into positive, cognitive, or negative symptoms. Despite the multiple clinical impairments in perception, cognitive deficits are now considered a core of the disease as they persist over time and have a high incidence among patients (Bowie and Harvey, 2006).

Several epidemiological and genetic studies have identified the role of inflammation and immunity in schizophrenia, with numerous infectious agents identified as risk factors and increased serum levels of pro-inflammatory cytokines and markers of endothelial cell activation (Khandaker and Dantzer, 2016; Müller, 2018). Indeed, a recent meta-analysis showed that patients with schizophrenia present with higher levels of pro-inflammatory mediators in the cerebrospinal fluid (Wang and Miller, 2018). Recently, P2RX7, P2RX4, and male P2RX5 mRNA expression were significantly increased in the dorsolateral prefrontal cortex of subjects diagnosed with schizophrenia, and a correlation between P2RX4 and P2RX7 mRNA and the inflammatory marker SERPINA3 was also reported, suggesting an association between upregulated P2XR and neuroinflammation in schizophrenia (Alnafisah et al., 2022). This dysregulation of the purinergic system in a brain region-dependent manner may have important implications in schizophrenia.

Microglia are resident macrophages and are the primary form of active immune defense in the CNS. Microglial activation triggers the release of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. MIA was shown to increase IL-6 expression in embryonic microglia in mid-pregnancy, although no marked changes in morphology were observed from E18 onwards. In the same study, MIA induced earlier (at E12) in pregnant mice caused sustained alterations in the patterns of microglial motility and behavioral deficits (Ozaki et al., 2020). Recently, genome-wide association studies have supported a causal relationship between immune dysregulation and schizophrenia in the post-mortem dorsoprefrontal cortex of patients with schizophrenia. These results highlight communication between the central and peripheral immune systems in schizophrenia (De Picker et al., 2021).

Chronic neuroinflammation is one of the leading underlying causes of schizophrenia progression. The P2X7 receptor, which is a significant driver of inflammation, is a key mediator of ATP release in astrocytes and activated microglia. Under psychological stress, glutamate is produced by neuronal cells, which mediates the astrocytes to release ATP into the extracellular space (Iwata et al., 2016), leading to a P2X7-mediated release of inflammatory cytokines and, ultimately, to an immune response. Using summary statistics from recent meta-analysis genome-wide association studies in patients with schizophrenia, a study identified significant enrichment of schizophrenia risk heritability in excitatory and inhibitory neurons. The P2X7 receptor has been identified as a strong candidate gene that drives a schizophrenia association signal (Trubetskoy et al., 2022). Regarding functional studies, the potential of the P2X7 receptor as a therapeutic target for cognitive symptoms in schizophrenia was investigated in an infant sub-chronic phencyclidine-induced model, where the P2X7 receptor protein expression increased in the hippocampus after treatment. However, its pharmacological blockade attenuated schizophrenia-like spatial memory impairments in rodents (Huang et al., 2021). Finally, whether inflammation during developmental stages influences the development of schizophrenia as a neurodevelopmental disease, purinergic modulation of subplate neuron activity has been proven as a potential explanation between MIA and disruptions in cortical development (Beamer et al., 2017), which might lead to cognitive disruptions in neurodevelopmental disorders such as autism or schizophrenia. In *Xenopus*

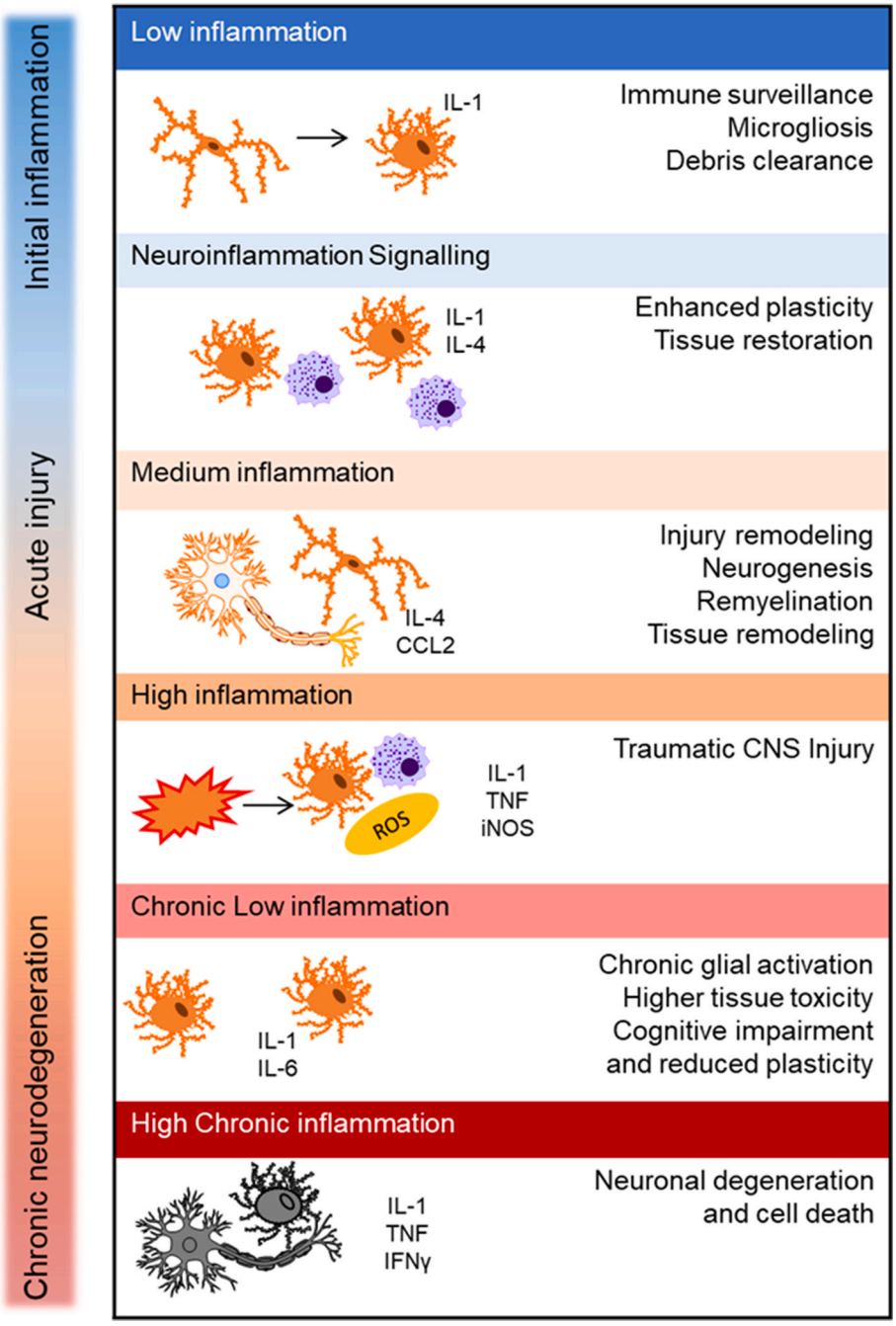


**Fig. 3. Span and intensity of an inflammatory reaction define whether it is beneficial or detrimental to the central nervous system (CNS).** Glial cells activate in local or systemic neuroinflammatory response to acute or chronic CNS damage. Controlled inflammatory reactions are generally beneficial for the maintenance of the health of the system after infection. For example, IL-1 and IL-4 are also crucial as signaling interleukins in maintaining brain plasticity. After an innate inflammatory response, leukocytes are recruited. IL-4-driven repolarization of macrophages has been proven to be highly advantageous in promoting recovery and axonal regrowth. When the inflammation becomes chronic after a traumatic CNS injury, significant recruitment and trafficking of peripheral macrophages and neutrophils to the site of injury are accompanied by cytokines (IL-1 and TNF), reactive oxygen species, and other inflammatory mediators (inducible nitric oxide synthase) leads to reduced neuronal plasticity and cognitive impairments. A higher degree of chronic inflammation significantly damages the nervous system and is characteristic of escalating toxicity and neuronal death.

*laevis* oocytes, P2X2 and P2X4 receptors interact with N-methyl--D-aspartate receptors (NMDARs), inhibiting NMDAR function. In particular, P2X4 receptor seems to act in a targeted manner inside the cell and around the post-synaptic area when stimulated (Rodriguez et al., 2020). This might contribute to the idea that calcium entry through P2X4 receptor plays a role in the induction of long-term potentiation (LTP) via NMDARs (Sim et al., 2006). In addition, mice lacking P2X4 receptors show sensorimotor gating impairments in the prepulse inhibition test (Wyatt et al., 2013). Deficient sensorimotor gating using prepulse inhibition of the acoustic startle reflex observed upon P2X4 receptor potentiation by ivermectin was significantly alleviated by dopaminergic receptor antagonists. This implies that stimulation of P2X4 receptor can lead to dopaminergic hyperactivity and disruption of information processing, suggesting P2X4 receptors as a novel drug target for the treatment of psychiatric disorders characterized by sensorimotor gating deficits (Khoja et al., 2019). P2X4 receptors are selectively upregulated in neurons and/or glia in various CNS disorders, including anxiety, chronic pain, epilepsy, ischemia, and neurodegenerative diseases. Pre- and post-synaptic dopaminergic markers were significantly altered in the dorsal and ventral striatum of P2X4 knockout (KO) mice, implicating altered dopamine neurotransmission (Khoja et al., 2016). These findings might be significant for several psychiatric disorders, such as schizophrenia, bipolar disorders, attention deficit hyperactivity disorder, and obsessive-compulsive disorder.

In addition to P2X receptors, P2Y1 receptors may also indirectly contribute to schizophrenia in postnatal life. A selective P2Y1 receptor agonist (MRS2365) infused into the medial prefrontal cortex negatively affects working memory and learning tasks in rats and has an ameliorating effect on the prepulse inhibition (PPI) of the acoustic startle

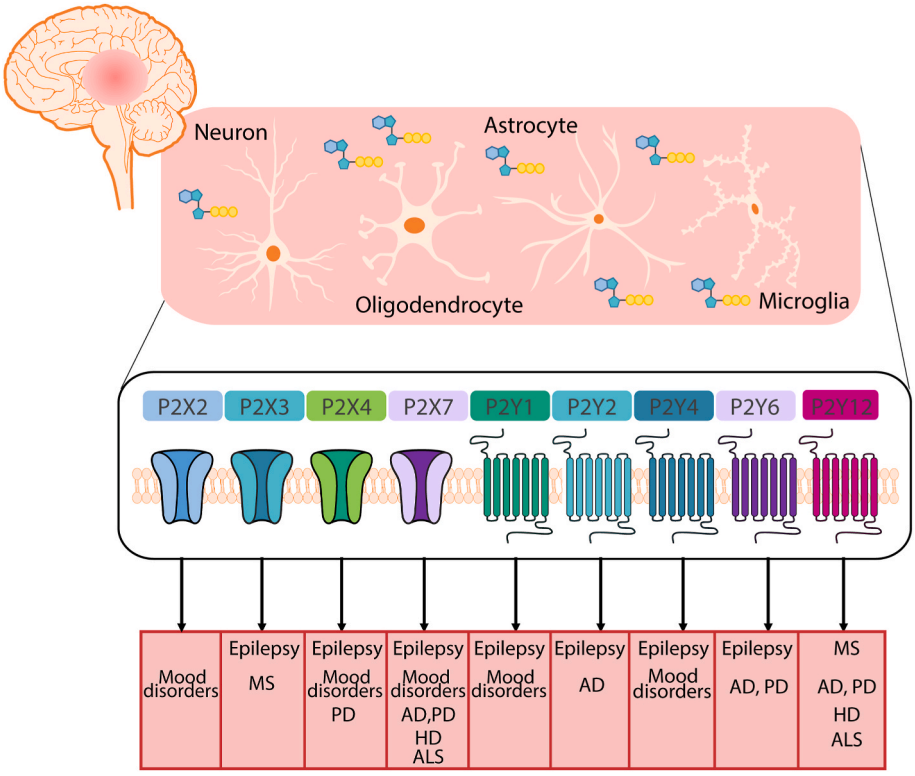


**Fig. 4. Schematic representation of the purinergic receptors during pathological conditions in the CNS.** During trauma, stroke, or heavy neuroinflammation, ATP and other metabolites function as a danger signal for the neuronal cells of the brain. Here we show the implication of each receptor in multiple diseases of the CNS.

reflex, which can be related to cognitive deficits and PPI observed in schizophrenia (Koch et al., 2015). Moreover, social isolation disrupts brain development and contributes to changes in adulthood. Indeed, in rats, purinergic receptor expression is modified, promoting increased expression of P2Y1 and P2X5 receptors in the prefrontal cortex and downregulating several purinergic components in the striatum (P2X4, P2Y2, P2Y6, P2Y12, and P2Y13 receptors) and hippocampus (P2Y4, P2Y13, and P2Y14), correlating with deficits in PPI (Andrejew et al., 2021).

*Autism spectrum disorder* (ASD) is characterized by deficits in communication and social interactions, restricted interests, and stereotyped behavior. Antipurinergic therapy corrects autism-like features in the Fragile X (*Fmr1* knockout) mouse model (Naviaux et al., 2015). Prenatal exposure to valproic acid (VPA) is associated with an increase in autism spectrum susceptibility. In an animal model of prenatal VPA, suramin, a non-selective purinergic antagonist, restored sociability in the three-chamber apparatus and decreased anxiety as measured by the elevated plus maze apparatus, suggesting a role of purinergic signaling in a neurodevelopmental model of autism spectrum disorder (Hirsch et al., 2020). Low-dose suramin in autism spectrum disorder showed improvements in language and social interaction and decreased restricted or repetitive behaviors in a small clinical trial of ten male subjects with the spectrum (Naviaux et al., 2017).

Recently, it was shown that ATP from astrocytes might regulate autism-like behavior in mice through P2X2 receptors in the prefrontal cortex and possibly through GABAergic synaptic transmission (Wang Q. et al., 2021).P2X4 deficiency enhances tactile sensitivity and significantly reduces social interaction and maternal separation-induced ultrasonic vocalizations in pups (Wyatt et al., 2013). These studies highlight P2X4 as a possible target for disturbances in the socio-communicative functions associated with neurodevelopmental disorders. Horváth et al. (2019) proved for the first time the role of the P2X7 receptor in an MIA induced autism-like behavioral model, where endogenous activation of the receptor is needed to develop an autistic phenotype. Recently, it was revealed that ATP activation of the P2X7 receptor results in downstream signaling pathways that also mediate the development of sociability deficits and repetitive behaviors in an MIA neurodevelopmental model of autism (Szabó et al., 2022). In a PIC model of MIA, immunoblot analysis of cerebral synaptosomes revealed a reduction in both P2X7 and P2Y12 receptor expression (Naviaux et al., 2013).

*Rett syndrome* is a rare neurodevelopmental genetic disorder that affects brain development, resulting in severe mental and physical disability. P2X7 receptor inhibition ameliorates dendritic spine pathology and social behavioral deficits in Rett syndrome mice (Garré et al., 2020).

## 8. P2 receptors in pathology: a shift from young adulthood to aging

The purinergic pathway mediates both pro-inflammatory and anti-inflammatory responses, with the breakdown of ATP to the extracellular process at a critical equilibrium. Whether neuroinflammation elicits beneficial or cytotoxic effects on the CNS depends on its intensity and duration (Fig. 3), which is a key regulatory event in both the physiology and pathology of the brain (DiSabato et al., 2016; Schwartz and Baruch, 2014).

Although many studies have explored the physiological aspects of the purinergic signaling system during development and in the adult brain, its role appears to be even more prominent under pathological conditions (Fig. 4).

KO mice and selective antagonists have been used to study pathological functions due to the malfunctioning of P2X receptors, such as taste (P2X2 receptor), pain/cough (P2X3 receptor), neuropathic pain (P2X4 receptor), and faulty immune reactions (P2X7 receptor) (Illes et al., 2020a). Other receptors, such as P2X1 and P2X5 receptors, have

received little attention because their function in adulthood, especially in the brain, still needs to be elucidated. Recently, the function and structure of the P2X5 receptor were reevaluated (King, 2022). In fact, contrary to the fetal brain, *in situ* hybridization experiments failed to show significant levels of P2X5 mRNA in adult rat brains, except for the mesencephalic nucleus, where mechanoreceptive sensory neurons of the trigeminal nerve (cranial nerve V) are found (Collo et al., 1996). A similar case occurs with the P2X6 receptor, which is less functionally present in postnatal development and the adult rat brain, forming heteromers with P2X4 (Lê et al., 1998). Recently, it has been demonstrated in the adult mouse hippocampus that non-glycosylated P2X6 receptors translocate to the nucleus, where they interact with the splicing factor (SF3A1), altering mRNA splicing (Díaz-Hernández et al., 2015). However, the mechanism and function of the P2X6 receptor in the adult brain require further investigation. Below, we provide a brief overview of the involvement of P2 receptor-mediated purinergic mechanisms in the most common brain pathologies.

### 8.1. Epilepsy

Epilepsy is one of the most common and disabling chronic neurological disorders characterized by recurrent spontaneous seizures, which can be focal (abnormal neuronal activity is localized in a brain region) or generalized (widespread distribution) in nature, caused by excessive or synchronous neuronal activity in the brain (Devinsky et al., 2018). The incidence of epilepsy tends to be the highest in infancy and early childhood and then in older groups (more than 50–60 years). The prevalence tends to be lowest in infants and children, increases in early adulthood and decreases later in life (Fiest et al., 2017). It has been demonstrated that P2X3 receptor activation may aggravate the hyperexcitability of neurons in the hippocampus, and P2X3 inhibition may have a remission effect in patients with intractable temporal lobe epilepsy and a rat model of epilepsy (Zhou et al., 2016). P2X4 receptor activation in neurons and microglia coincide with pathological neuronal states. In a mouse model of kainate-induced status epilepticus, P2X4 receptor was shown to play a role in neuronal hyperexcitability by controlling specific aspects of microglial activation, suggesting that P2X4 receptor contributes to excitotoxic damage during status epilepticus (Ulmann et al., 2013). Following status epilepticus induced by intra-amygdala kainic acid in both wildtype and P2X7-KO mice, genome-wide microRNA profiling showed a distinct pattern of microRNA expression in hippocampal tissue, particularly those associated with inflammation and cell death (Conte et al., 2020). In a transgenic overexpressing eGFP-P2X7 mouse, after status epilepticus, P2X7 expression in microglia and oligodendrocytes increased in the hippocampus, cortex, striatum, thalamus, and cerebellum, converting P2X7 receptor as a hallmark of acute seizures and epilepsy (Morgan et al., 2020).

Recently, P2Y receptors were implicated in the pathogenesis of epilepsy during seizures. Western blotting at different time points post-status epilepticus in the epileptic ipsilateral cortex revealed a differential increase in the expression of several P2Y receptors, such as P2Y1, P2Y2, P2Y4, and P2Y6. Specifically, P2Y1 receptor showed the highest increase, which was demonstrated to be microglial specific. Moreover, a P2Y1-antagonist was found to reduce seizure severity during status epilepticus and protect against cortical damage (Alves et al., 2020). Interestingly, the same group demonstrated that P2Y1 receptor activation is context-specific during seizures, switching from a proconvulsive to an anticonvulsive role. Blockage of P2Y1 receptor before a chemoconvulsant exacerbates epileptiform activity. In contrast, if it is targeted during status epilepticus, the development of epilepsy and associated brain damage is delayed, and spontaneous seizures in mice are suppressed (Alves et al., 2019). This was corroborated in human hippocampal samples with temporal lobe epilepsy, which showed an increase in P2Y1 and P2Y2 protein levels and a decrease in P2Y13 protein levels (Alves et al., 2017).

### 8.2. Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating neurological disease that affects young adults. MS is associated with muscle weakness and is characterized by an autoimmune inflammatory reaction to myelin, resulting in oligodendrocyte death and demyelination and progressive irreversible axonal damage (Dobson and Giovannoni, 2019). In a recent genetic analysis of P2RX7 and P2RX4 receptors in patients with MS, a *P2RX7-P2RX4* haplotype containing three rare missense mutations in a multi-incident family with a high incidence of MS, which impairs the P2X7 receptor scavenger function, was identified, pointing to both P2X7 and P2X4 receptors as key players in the onset of MS (Sadovnick et al., 2017).

In an experimental autoimmune encephalomyelitis (EAE) model, P2X4 receptor activation with ivermectin led to a microglia/macrophage switch to an anti-inflammatory phenotype and increased brain-derived neurotrophic factor (BDNF) release, which ameliorated clinical symptoms, and promoted oligodendrocyte differentiation. Consequently, it has been hypothesized that P2X4 receptor indirectly promotes remyelinating responses (Zabala et al., 2018). A recent study used a cuprizone mouse model of T-cell-independent myelin degeneration to investigate remyelination. First, a dynamic increase in P2X7 receptor expression and signaling was observed during primary demyelination and remyelination, whereas deficiency of the receptor attenuated both inflammation and demyelination. P2X7 receptor induction in demyelinated tissue was paralleled by the robust upregulation of *Nlrp3*, *Asc,* and *Il1b*, which are known inflammasome-associated genes. However, in the same study, it was observed that the P2X7 receptor potential as a therapeutic target was limited, as pharmacological blockade of the receptors was insufficient to attenuate inflammation and promote the repair of degenerated myelin (Bernal-Chico et al., 2020). The role of P2X7 receptor and P2Y1 receptors in oligodendrocyte differentiation, as the main purinergic receptors active in oligoprogenitors, has also been discussed as a possible therapy to stimulate myelin repair in MS (Agresti et al., 2005; Lecca et al., 2021).

In the human MS frontal cortex, P2Y12 is present in myelin and interlaminar astrocytes, but its expression is altered at the axon-myelin interface in the white and gray matter of patients, which seems to be inversely proportional to demyelination and lesion formation, indicating that a reduction in P2Y12 receptor might serve as a marker for developing MS (Amadio et al., 2010). Recently, in EAE and MS post-mortem tissues, it was shown that, while high expression of P2X7 receptor in microglia is associated with a pro-inflammatory phenotype of human MS lesions, P2Y12 receptor was associated with an anti-inflammatory phenotype instead of being expressed at lower levels in active inflammatory MS lesions, and its higher expression was associated with the remission phase of EAE (Beaino et al., 2017).

### 8.3. Pain

Sensory information, such as pain, taste, or touch, is transduced by various nerve endings and is transmitted to the spinal cord via the dorsal root and trigeminal ganglia. These afferents have cell bodies in the nodose ganglion that project to the nucleus of the solitary tract in the brainstem. P2X2 and P2X3 receptors are widely expressed in peripheral nerves, system sensory functions, and the CNS. P2X3-P2X2/3 receptors are expressed in nociceptive neurons and sensory and sympathetic ganglion neurons, which are attractive targets for many pain-related diseases and mechanosensory transduction (Cockayne et al., 2005). P2X1 and P2X3 receptors are also present in adult rat DRG neurons and small-to-medium-sized nodose ganglion neurons with fast activated and rapidly activated desensitized currents. P2X2 and P2X4 receptors are located primarily on medium- and large-sized nodose ganglion neurons with fast activated and slow-desensitized currents (Wang et al., 2014). In an electrophysiological study in a rat model of nerve injury, the specific P2X3 and P2X2/3 antagonists A-317491 had an antinociceptive effect

on dorsal horn neural responses, suggesting a role for P2X3 and P2X2/3 receptors in neuropathic pain (Sharp et al., 2006). Neurological damage caused by a lesion or disease of the somatosensory nervous system often leads to chronic pathological and neuropathic pain. There are no effective treatments for this condition owing to its complex pathogenesis, which is associated with progressive hyperpathia and hyperesthesia. Neuropathic pain can be categorized as either peripheral (PNP) or central, where the main difference is the location of nerve injury or disease (Finnerup et al., 2021).

Recently, it has been pointed out that G protein-coupled receptor 151 (GPR151), which is a nociceptive sensory system coupled with P2X3 receptor, may be responsible for neuropathic pain-like hypersensitivity in DRG neurons. In Gpr151 KO, P2X3-mediated calcium elevation and spontaneous pain behavior were suppressed in mice with chronic constriction injury (Xia et al., 2021). Hyperalgesia caused by damage to nociceptors or peripheral nerves results in an abnormally increased sensitivity to pain or hypersensitivity to stimuli, presenting as chronic pain. In heroin self-administered rats, the expression of P2X2 and P2X3 receptors in the dorsal root ganglia increased in correlation with thermal hyperalgesia and mechanical allodynia (Leng et al., 2018). Moreover, the development and maintenance of chronic-latent mechanical muscle hyperalgesia seem to be modulated by P2X3 receptors on the dorsal horn of the spinal cord of mice, interacting with protein kinase C epsilon (PKCε), which is a well-known hyperalgesia mediator transiently activated in chronic muscle pain (Jorge et al., 2020). In a rat model of sciatic nerve chronic constriction injury, retrograde trace labeling combined with immunofluorescence technology recently showed the upregulation of P2X3 receptor subtypes in medium neuropathic nociceptive DRG neurons combined with the downregulation of P2X2 cells in neuropathic nociceptive small DRG neurons. Simultaneously, the expression of other receptors was invariable, indicating that both modulate nociceptive sensitivity (Chen et al., 2020). Moreover, chronic visceral hyperalgesia following exposure to post-stress disorders is associated with higher expression of P2X3 receptor and potentiated ATP-evoked responses in DRG sensory neurons (He et al., 2017). In addition, P2X4 receptor is upregulated in the satellite glial cell marker glial fibrillary acidic protein in the dorsal root ganglia in a rat model of neuropathic pain (Wang M. et al., 2021). Mice lacking P2X4 receptors do not develop pain hypersensitivity or prostaglandin E2. This inflammatory mediator contributes to pain hypersensitivity by promoting the hyperexcitability of sensory neurons (Ulmann et al., 2010).

Recently, the relationship between inflammation and acute pain hypersensitivity was studied with brief exposure to tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine, in rat hind paws, which rapidly increased P2X3-mediated inward currents in a dose-dependent manner. Moreover, this synergy was blocked by a p38 mitogen-activated protein kinase inhibitor, indicating a putative new pathway that requires further investigation (Jin et al., 2021). P2X4 receptor is often associated with neuropathic pain in the CNS, mainly through the activation of microglia and recruitment of receptors by the release of damage factors (such as TNF-α) and ATP, which ultimately leads to enhanced excitability of synapses and increased sensory nerve signal transmission and pain (De Macedo et al., 2019). Finally, among all the P2X receptors, P2X7 receptors target inflammatory diseases, and there is a well-established link between inflammation and neuropathic pain (Ren and Illes, 2022).

The implications of P2Y receptors, particularly P2Y1, P2Y2, P2Y6, P2Y12, and P2Y13, in neuropathic pain have recently been comprehensively reviewed (Zhang and Li, 2019). In a chronic mice model of neuropathic pain, P2Y14 receptor was also proven to be effective in reversing neuropathic pain from peripheral nerve injury in a dose-dependent manner (Mufti et al., 2020). Furthermore, in trigeminal neuropathic pain, a type of PNP, P2Y14 receptor, has recently been identified as a putative novel therapeutic target, as mechanical hypersensitivity was accompanied by the upregulation of P2Y14 receptor in an orofacial neuropathic pain model in trigeminal ganglion neurons and satellite glial cells (Lin et al., 2022).

### 8.4. Mood disorders

Mood disorders comprise mental disorders that affect the emotional state, causing persistent and intense sadness, intense happiness, or both, and/or other persistent emotions such as irritability and anger. These include major depression, anxiety, and bipolar disorder and their subtypes. ATP is a critical factor involved in the astrocytic modulation of depressive-like behavior in a model of chronic social defeat in adult mice. In particular, P2X2 receptors appear to mediate the antidepressant-like effects of ATP in the medial prefrontal cortex (Cao et al., 2013). In the CNS, while P2X2 and P2X3 receptors showed normal behavior and motor function, ATP infusion in the medial prefrontal cortex showed that P2X2 receptor was the only one responsible for mediating ATP modulation of the passive coping response to behavioral challenge (Kong et al., 2020). Moreover, in a recent study of subjects who had major depression that either attempted suicide or not attempted suicide, and healthy volunteers, a relationship between P2X2 mRNA expression and depression was found (Zheng et al., 2023). Recently, P2X4 receptor density in the hippocampus was altered during LTP and long-term depression (LTD) plasticity phenomena at CA1 synapses without affecting basal excitatory transmission in a conditional transgenic knock-in P2X4 mouse line, driving anxiolytic effects and deficits in spatial memory (Bertin et al., 2021). Perioperative neurocognitive disorder is a frequent difficulty after surgery, which consists of deterioration of perioperative memory, attention, executive ability, language ability, and other cognitive functions. In mice undergoing open tibial fracture surgery by sevoflurane anesthesia, animals showed cognitive impairment in the Morris water maze three days after anesthesia, increased expression of P2X4R and NLRP3, and aggravated neuroinflammation and microglial activation (Yuan et al., 2022). Imipramine, a tricyclic antidepressant, reduced P2RX7 and P2RX4 levels in the ventral hippocampus of rats, together with the antidepressant-like behavior observed in the learned helplessness paradigm with repeated treatment of a P2RX7/P2RX4 antagonist, showed that pharmacological blockade or decrease in the expression of P2RX7 might be a possible therapeutic target for depressive-like behaviors (Ribeiro et al., 2019).

Over the past ten years, the P2X7 receptor has been identified as an emerging therapeutic target for treating mood disorders as a significant driver of inflammation. The P2X7 receptor seems to be a key mediator of ATP release in astrocytes and activated microglia, which might drive functional changes due to its role in multiple signal transduction pathways, consequently leading to depressive-like reactions in depression and bipolar disorder (Illes et al., 2020b). Under psychological stress, glutamate is produced by neuronal cells, which mediate the astrocytes to release ATP into the extracellular space (Iwata et al., 2016), followed by the release of inflammatory cytokines, and ultimately to an immune response mediated by the P2X7 receptor. High extracellular ATP levels and sustained receptor activation lead to pore formation (Di Virgilio et al., 2018). Consequently, the efflux of intracellular components will, in turn, maintain elevated ATP levels in the extracellular space, which will continuously activate the P2X7 receptor and eventually lead to cell death. Therefore, both the regulatory role of the P2X7 receptor in the inflammatory response and as a promoter of the immune response position the receptor as a potential therapeutic target in psychiatric diseases. In addition, P2X7 receptors mediate the modulation of 5-HT release from the hippocampal terminals of the median raphe region, suggesting a potential role for the receptor in the modulation of cognitive and affective functions, and ultimately in psychiatric and mood disorders (Gölöncsér et al., 2017). In male Sprague-Dawley rats subjected to chronic unpredictable stressors, treatment with P2X7 receptor antagonists stopped the development of depression-like behaviors induced by chronic unpredictable stress in rats (Yue et al., 2017). In another study of mice subjected to contextual fear conditioning, genetic or pharmacological blockage of the P2X7 receptor increased contextual

fear recall, promoting anxiogenic-like effects and deficits in extinction learning (Domingos et al., 2018). The P2RX7 gene is located on chromosome 12 at 12q24.31 and encodes the P2X7 receptor. Variations in P2RX7 have previously been associated with a higher risk of several psychiatric disorders (McGuffin et al., 2005). Linkage studies correlated P2RX7 variants with depressive symptoms in two independent patient samples (Vereczkei et al., 2019). Recently, a linkage study investigated the effect of P2X7 single-nucleotide polymorphism in interaction with childhood stress on the development and severity of depressive symptoms (Kristof et al., 2021).

P2Y1 receptors have been observed in neurons in the hypothalamus, amygdala, hippocampus, and periaqueductal gray, and stimulation of these receptors causes anxiolytic-like effects in the elevated plus-maze in rats, suggesting a role in the modulation of anxiety (Kittner et al., 2003). Recently, genetic deficiency in P2Y12 receptor mice was found to result in altered anxiety, deficits in memory, and reduced locomotion, together with decreased noradrenaline levels and noradrenergic α receptor expression in the mouse cerebellum and hippocampus (Zheng et al., 2019). In fact, in patients with major depressive disorder, a single-cell mass cytometry of microglia detected a generalized increase in the levels of the homeostatic protein P2Y12 receptor (Böttcher et al., 2020).

### 8.5. Ethanol intake

Reduced expression of P2X4 in the nucleus accumbens significantly increases ethanol intake and preference, supporting the hypothesis that P2X4 plays a role in the regulation of ethanol intake (Khoja et al., 2018). P2X4R–KO mice exhibit deficits in sensorimotor gating, social interactions, and ethanol drinking behavior (Wyatt et al., 2014). Alcohol-preferring rats have a lower functional expression of the *p2rx4* gene than alcohol-non-preferring rats, suggesting that P2X4 receptors are involved in the development and progression of alcohol use disorders in an inverse relationship between alcohol intake and P2X4 receptor expression (Franklin et al., 2014). Changes in P2RX4 expression due to ethanol intake in developing microglia could deregulate purinergic and fractalkine signaling, two different mechanisms of neuron-microglia crosstalk that may impact synaptic plasticity (Gofman et al., 2014).

### 8.6. Neurodegenerative disorders

Neurodegenerative disorders (ND) are characterized primarily by neuronal loss. The most common ND involve neurodegeneration as their hallmark, with Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) being the most common ones, followed by motor neuron disease, spinal muscular atrophy, and spinocerebellar ataxia. Age seems to be the most contributing factor to the development of most ND, although it might also be a combination of environment and individual genetic expression (Lamptey et al., 2022).

HD is an autosomal dominantly inherited neurodegenerative disease that appears in middle age (30–50 years old) and is characterized by the expansion of repeated CAG triplets in the huntingtin gene. This encodes an expanded polyglutamine (polyQ) stretch and consequent production of an abnormal huntingtin protein, resulting in neuronal dysfunction and death, especially in the striatum, provoking hyperkinetic symptoms and motor disturbances (McColgan and Tabrizi, 2018). Recently, in the post-mortem striatum of the brains of people with HD, both mRNA and P2X7 protein levels were upregulated, demonstrating that the P2X7 receptor might be a potential target for the diagnosis or treatment of HD. Interestingly, alterations in its splicing were also observed, showing that P2X7 introns 10 and 11 were retained more in patients with HD than in controls (Ollà et al., 2020). In hiPSC-derived NPC from HD and control subjects, spontaneous alterations in calcium responses evoked by ATP upon maturation and survival of GABAergic neurons were altered together with a significant decrease in the 2SUTP response, an agonist of the P2Y2 receptor. These data might correspond to the impairment of P2Y2 receptor activation in HD, which requires further investigation (Glaser et al., 2021a)

ALS is a progressive adult-onset (40–60 years of age) neurodegenerative disease characterized by upper and lower motor neuron loss in the cerebral cortex, brainstem, and spinal cord. Purinergic involvement in ALS has been reviewed widely on a large scale, driving exacerbated glial responses and maintaining neuroinflammatory conditions, among which P2X4 and P2X7 receptors have received more attention (Volonté et al., 2011). Several misfolded proteins related to ALS, such as SOD1 and TDP-43, are associated with a significant increase in the surface of P2X4 receptor. Recently, in the spinal cord of SOD1-G93A (SOD1) mice, a higher density of P2X4 receptor was observed in the peripheral macrophages of SOD1 mice before the onset and during the progression of ALS, positioning P2X4 receptor as a potential hallmark of the disease (Bertin et al., 2022). Moreover, following the chronic activation of microglia due to neuroinflammation, continuous activation of the P2X7 receptor is triggered. Recently, chronic administration of a P2X7 receptor antagonist delayed disease onset and progression and improved motor coordination in ALS $SOD1^{G93A}$ female mice (Ruiz-Ruiz et al., 2020).

It has been identified that P2Y12 receptor is a possible pivotal receptor for ALS (Butovsky et al., 2014). The direct relationship between P2Y12 receptor and active microglia in pathological conditions leads to the hypothesis that P2Y12 receptor may play a role in the pathogenesis of ALS. G protein-coupled receptor 17 (GPR17) is a P2Y-like metabotropic receptor associated with oligodendrocyte differentiation, and its role in counteracting oligodendrocyte dysfunction in ALS was recently studied in an ALS SOD1 mouse model, validating the idea that the purinergic system is involved in the progression of this disease (Bonfanti et al., 2020).

PD is the second most common neurodegenerative disease, with a higher incidence in people over 80 years of age. Akin to HD, PD is a neurodegenerative disorder characterized by dopaminergic and GABAergic neuronal death in the basal ganglia, leading to hypokinetic symptoms, striatal dopamine deficiency, and intracellular inclusions of α-synuclein aggregates. The P2X4 receptor is an ATP-gated ion channel that is widely expressed in microglia, astrocytes, and neurons of the CNS and PNS. Recently, in a rat model of PD, the inhibition of the P2X4 receptor reduced the rotation behavior induced by apomorphine treatment and significantly reduced classical selective autophagy receptor levels, such as p62 and tyrosine hydroxylase, a BDNF, LC3-II/LC3-I, and phosphorylated tropomyosin receptor kinase B (TrkB) in brain tissue, indicating a role of neuronal autophagy through the regulation of the BDNF/TrkB signaling pathway (Zhang et al., 2021). Large amounts of extracellular ATP and UDP released by dying cells may activate the P2X7 receptor, leading to microglial activation, among other purinergic receptor subtypes. Recently, increased activation of the P2X7 receptor was found in a rat model of PD, promoting the release of cytokines, nitric oxide, and reactive oxygen species from microglia and affecting viable neurons (Oliveira-Giacomelli et al., 2019). Recently, the role of the P2X7 receptor in microglia has been extensively studied, showing that the P2X7 receptor is overexpressed in an acute rather than a progressive rat model of PD (Crabbé et al., 2019). P2X1 has been proposed as a new target of the disease as the P2X1 receptor mediates the increase in intracellular accumulation of alpha-synuclein induced by extracellular ATP *in vitro* (Gan et al., 2015).

In a recent genetic association data study, microglial dysregulation was shown to be an important factor for PD, and P2RY12 as the most likely driver and pathogenic player in PD (Andersen et al., 2021). Interestingly, in a mouse model of PD, P2Y12R was found to potentially contribute to the activation of microglia and the progression of the disease in a dualistic manner, depending on the stage of neurodegeneration. While P2Y12 receptors seem to be essential for initiating a protective inflammatory response as either pharmacological or genetic blocking of P2Y12 receptor augments acute mortality in MPTP-treated

**Box 1**
Remaining question

Purinergic signaling modulates both embryonic neurodevelopmental pathology and neurodegeneration in young adult and older subjects. When do the purinergic receptors switch from physiologically necessary to pathological targets in the CNS?

mice, at later stages of neurodegeneration, P2Y12 receptors are apparently responsible for maintaining the activated state of microglia and stimulating pro-inflammatory cytokine response (Iring et al., 2022). Moreover, an increase in UDP might activate the P2Y6 receptor, supposedly inducing phagocytosis via reactive microglia (Oliveira-Giacomelli et al., 2019). Thus, the level of this receptor in peripheral blood mononuclear cells was measured in PD, showing higher expression levels of the P2Y6 receptor. This indicates that P2Y6 receptor may also be an important target for PD, although further investigation is needed (Yang et al., 2017).

AD is a tauopathy family of ND characterized by the presence of aberrant intraneuronal aggregates of hyperphosphorylated microtubule-associated proteins. In a new study in patients with different tauopathies and a tauopathy mouse model, overexpression of the P2X7 receptor was observed in microglia, which caused memory deficits and aggravated tau-derived toxicity in mice (Di Lauro et al., 2022). Microglia, the resident phagocytes of the CNS, play an important role in the pathogenesis of neurodegenerative diseases. Regarding P2Y receptors, in the post-mortem neocortex of patients with AD, a severe decrease in immunoreactivity was found in the parietal cortex (Lai et al., 2008). Interestingly, the antagonistic role of P2X7 and P2X2 receptors in ND has been discussed, showing that a balance between P2Y2R and P2X7R is crucial for healthy communication between neural cells (Glaser et al., 2021b).

UTP released from stressed neurons activates the microglial P2Y6 receptor, inducing phagocytosis of neurons. Still, it has also been shown to phagocytize isolated synapsis, which seems to be important in age-associated synaptic loss. Blockage of P2Y6 receptor was shown to prevent LPS-induced synaptic loss in glial–neuronal co-cultures, which suggests that P2Y6 receptor might be involved in age-associated memory loss and can be targeted to prevent associated cognitive deficits (Dundee et al., 2022). Microglial phagocytosis is important in neurodegenerative diseases, including AD. Injection of amyloid beta (Aβ) into the mouse brain induces microglial phagocytosis of neurons, followed by neuronal and memory loss, which is halted in P2Y6R–KO mice. Similarly, *P2ry6* KO appears to have a protective role against TAU-, Aβ-, and UDP-induced neuronal loss *in vitro*. Finally, in a TAU model of neurodegeneration, *P2ry6* KO mice showed reduced neuronal loss and memory deficits (Puigdellívol et al., 2021). Recently, the expression of P2Y12 receptor in microglia has been studied in both AD and non-AD tauopathy patients and tauopathy model mice, with a decrease in the expression of the receptor in regions enriched with tau inclusions, despite an increase in the total microglial population reported (Maeda et al., 2021). P2Y12 receptors have been detected in hippocampal microglia with dystrophic morphology, shorter protrusions, and foamed cell bodies in human brains with AD compared to age-matched control brains (Mildner et al., 2017).

## 9. Concluding remarks

At the initial stages of purinergic system development, a high degree of complexity (enzyme and receptor diversity and multiple roles) is expected, although the systems mature from development to adulthood. Especially during the development of the brain, extracellular ATP, nucleotides, and nucleosides are higher, as they need to regulate many neural processes. Progressively, a switch occurs when ATP signals become a a marker for pathology and neuroinflammation in the adult brain. This review emphasizes the complexity of the purinergic system observed in the responses of different receptors to ATP and other metabolites and the dual role of purinergic receptors in physiology and pathology in an individual's life course. Based on this functional dichotomy of purinergic receptors in physiology and pathology, we speculate that ATP levels within a neuronal system may regulate both conditions because of their integrated roles as intracellular second messengers in biology.

P2 receptors are becoming more relevant as therapeutic targets for several pathologies, from neurodevelopmental disorders to adult disorders, such as epilepsy, MS, and ND. However, further investigations are needed to understand the different and opposite roles of the receptors over one's lifespan to either promote neurogenesis, migration, and synapsis if needed or decrease neuroinflammation in certain disorders. It is especially critical for neurodevelopmental disorders to approach P2 receptors in a conditional matter to determine whether neuroinflammation occurs during gestation and brain formation, as they are crucial for proper development (see box 1). This might not be the case for diseases in adulthood when targeting P2 receptors as a preventive measure of neuroinflammatory processes might be indispensable for developing a neurological disorder.

## Declaration of competing interest

The authors declare no conflicts of interest.

## Data availability

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

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