Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Brain, Behavior, and Immunity 89 (2020) 480–490

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Purinergic signaling in infectious diseases of the central nervous system

Vinícius Santos Alves[1], Raíssa Leite-Aguiar[1], Joyce Pereira da Silva, Robson Coutinho-Silva, Luiz Eduardo Baggio Savio[*,2]

Laboratory of Immunophysiology, Biophysics Institute Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

ARTICLE INFO

Keywords:
Neuroinfections
Neuroinflammation
Cerebral toxoplasmosis, Zika, SARS-CoV-2
P2 receptor
CD39
CD73
Adenosine

ABSTRACT

The incidence of infectious diseases affecting the central nervous system (CNS) has been increasing over the last several years. Among the reasons for the expansion of these diseases and the appearance of new neuropathogens are globalization, global warming, and the increased proximity between humans and wild animals due to human activities such as deforestation. Neurotropism affecting normal brain function is shared by organisms such as viruses, bacteria, fungi, and parasites. Neuroinfections caused by these agents activate immune responses, inducing neuroinflammation, excitotoxicity, and neurodegeneration. Purinergic signaling is an evolutionarily conserved signaling pathway associated with these neuropathologies. During neuroinfections, host cells release ATP as an extracellular danger signal with pro-inflammatory activities. ATP is metabolized to its derivatives by ectonucleotidases such as CD39 and CD73; ATP and its metabolites modulate neuronal and immune mechanisms through P1 and P2 purinergic receptors that are involved in pathophysiological mechanisms of neuroinfections. In this review we discuss the beneficial or deleterious effects of various components of the purinergic signaling pathway in infectious diseases that affect the CNS, including human immunodeficiency virus (HIV-1) infection, herpes simplex virus type 1 (HSV-1) infection, bacterial meningitis, sepsis, cryptococcosis, toxoplasmosis, and malaria. We also provide a description of this signaling pathway in emerging viral infections with neurological implications such as Zika and SARS-CoV-2.

1. Introduction

Infectious diseases that affect the central nervous system (CNS) have been increasing in incidence over the last several years (Nath, 2015). Possible factors that contribute to the increased incidence and emergence of new pathogens that cause neuroinfections include globalization, climate change, and the increased contact of humans with wild animals (Daniel et al., 2018; Mackenzie, 2005). Several pathogenic organisms, including viruses, bacteria, fungi, and parasites, can present considerable neurotropism for the CNS, generating neuroinflammation and neurodegeneration (Cain et al., 2019). Neuroinfectious diseases create an inflammatory microenvironment that may have negative consequences on the quality of life and social activities of infected individuals, including cognitive dysfunction, behavioral changes,

Abbreviations: ACE2, Angiotensin-converting enzyme 2; ADO, Adenosine; ADP, Adenosine diphosphate; AIDS, Acquired immunodeficiency syndrome; AMP, Adenosine monophosphate; ARDS, Acute respiratory distress syndrome; ATP, Adenosine Triphosphate; BBB, Blood-brain barrier; BBG, Brilliant Blue G; BCSFB, Blood-cerebrospinal fluid barrier; BMDM, Bone marrow-derived macrophage; CAT, Catalase enzyme; CBD, Cannabidiol; CCL2, Chemokine (C–C motif) ligand 2; E-NTPDase, Ecto-nucleoside triphosphate diphosphohydrolase; CD73, Ecto-5′-nucleotidase; CLP, Cecal ligation and puncture; CNS, Central Nervous System; COVID-19, Coronavirus disease 2019; DV, Dengue virus; GP120, Envelope glycoprotein 120; HIV, Human immunodeficiency virus; HSV-1, Herpes simplex virus type 1; ICAM-1, Intercellular adhesion molecule 1; IL, Interleukin; INF-γ, Interferon gamma; ME49, Type 2 *Toxoplasma gondii* strain; MS, Multiple sclerosis; NLRP3, Nucleotide-binding domain leucine-rich repeat (NLR) and pyrin domain containing receptor 3; NMS, Neuroleptic malignant syndrome; NO, Nitric oxide; Ox-ATP, Oxidized ATP; P1, Purinergic P1 receptors; P2, Purinergic P2 receptors; PM, Pneumococcal meningitis; PNS, Peripheral nervous system; POM-1, Sodium polyoxotungstate; RH, Type 1 Toxoplasma gondii strain; RNS, Reactive nitrogen species; ROS, Reactive Oxygen Species; SAE, Sepsis Associated Encephalopathy; SARS-COV-2, Severe acute respiratory syndrome coronavirus 2; ShRNA, Short hairpin RNA; SOD, Superoxide dismutase; TAT, HIV trans-activator of transcription; THP1, Human monocytic cell line; TMEV, Theiler's murine encephalomyelitis virus; TNF-α, Tumor Necrosis Factor alpha; UDP, Uridine diphosphate; VCAM-1, Vascular cell adhesion molecule-1; WT, Wild type; ZIKV, Zika virus

[*] Corresponding author at: Instituto de Biofísica Carlos Chagas Filho – Universidade Federal do Rio de Janeiro, Edifício do Centro de Ciências da Saúde, Bloco G. Av. Carlos Chagas Filho, 373. Cidade Universitária, Ilha do Fundão, Rio de Janeiro, RJ 21941-902, Brazil.
E-mail address: savio@biof.ufrj.br (L.E.B. Savio).
[1] These authors have contributed equally to this work.
[2] ORCID ID: 0000-0002-6712-6885.

https://doi.org/10.1016/j.bbi.2020.07.026
Received 9 June 2020; Received in revised form 18 July 2020; Accepted 20 July 2020
Available online 24 July 2020

depression, seizures, and physical impairments. Despite these harmful outcomes, neurological symptoms verified in infectious diseases that affect CNS are usually neglected (Bruzzone et al., 2009).

The endothelial blood–brain barrier (BBB) is the primary regulation point for the entrance of circulating immune cells and pathogens within the CNS (Daneman and Prat, 2015). The BBB is formed by tight junctions between endothelial cells, pericytes, and astrocytes (Liebner et al., 2018). In addition to the BBB, other cellular and acellular barriers that separate the brain from the periphery include the arachnoid barrier and the blood-cerebrospinal fluid barrier (BCSFB). All these specific and protective segments explain the varying immunological interactions between the CNS and the peripheral nervous system (PNS) (Daneman and Prat, 2015; Engelhardt et al., 2017).

The blood–brain barrier, together with an absence of lymphatic vessels, constituted an anatomical peculiarity that characterized the CNS as an immune-privileged site, where undesired inflammatory processes are inhibited (Carson et al., 2006). Functional initial afferent lymphatic vessels in the outermost layer of the meninges in the CNS were described in 2015. This paradigm displaced the immune privilege hypothesis (Louveau et al., 2015). Subsequently, the presence of lymphatic vasculature in the CNS gave rise to the immunomodulatory parenchymal competence concept within the CNS (Engelhardt et al., 2017).

Blood-borne pathogens can cross the BBB to reach the CNS, generating a disruptive inflammatory scenario. They penetrate the barrier via transcellular or paracellular pathways, or through infected leukocytes—the “Trojan horse” method. Some pathogens can also circumvent the barriers and access the CNS through peripheral nerves by axonal transport (Dando et al., 2014). Finally, pathogens may benefit from immunomodulatory competence that protects them from immune cell activity. This phenomenon impairs complete pathogenic clearance, thereby permitting establishment of latent infections (Engelhardt et al., 2017).

The immune system establishes a relationship with the CNS to maintain homeostasis. The CNS presents limited degrees of innate and adaptive immunity; however, in the CNS parenchyma, microglia are the primary resident immune cells; these cells originate early in embryonic development (Ginhoux et al., 2010). They are immediately activated after infection, thereby promoting neuroinflammation. Excessive inflammation stimulates cell death and excitotoxicity, leading to dangerous consequences such as neurodegeneration (Engelhardt et al., 2017; McCusker and Kelley, 2013).

Excitotoxicity can be caused by excessive or prolonged extracellular accumulation of excitatory neurotransmitters, such as ATP and glutamate in particular (Cisneros-Mejorado et al., 2014; Olloquequi et al., 2018; Vermehren et al., 2018). Inflammatory events increase glutamate release by glial cells, inducing over-activation of glutamatergic receptors such as the N-methyl-D-aspartate (NMDA) receptor (Haroon et al., 2017; Olloquequi et al., 2018). The over-activation of these receptors abnormally increases intracellular Ca^{+2} concentrations, triggering the production of reactive oxygen and nitrogen species and reducing the energy metabolism of cells (Olloquequi et al., 2018). The production of free radicals and the decreased production of ATP affects the activity of membrane ion pumps, such as the Na^+,K^+-ATPase, which is crucial for maintaining the Na^+ gradient for glutamate uptake (Olloquequi et al., 2018). These events contribute to potentiation of extracellular glutamate accumulation and excitotoxicity. In addition, the loss of ionic homeostasis induces cell damage, death, and degeneration (Haroon et al., 2017; Olloquequi et al., 2018)

In addition to glial cells, circulating immune cells can be recruited to brain parenchyma to control the infection when the endothelial barriers are impaired (Prinz and Priller, 2017). This migration is a cell-dependent and barrier-dependent process that is usually mediated through blood vessels localized under the arachnoid barrier (Cain et al., 2019). These neuroinflammatory and neurodegenerative processes, and also the immune response to pathogens, involve several signaling pathways, including purinergic signaling (Di Virgilio et al., 2009; Savio et al., 2018; Savio and Coutinho-Silva, 2019).

Purinergic signaling is an evolutionarily conserved cell communication mechanism mediated by extracellular nucleotides and nucleosides (Burnstock and Verkhratsky, 2009). In 1929, the first study related to purinergic signaling was published presenting adenosine (ADO) as a molecule functionally similar to adenylic acid in the cardiovascular system (Drury and Szent-Gyorgyi, 1929). In the early 1970s, a seminal study described ATP and related compounds as signaling molecules in the nervous system of the gut (Burnstock et al., 1970). Shortly thereafter, the purinergic hypothesis was proposed (Burnstock, 1972). The importance of nucleotides for cell communication in various organ systems is currently well defined: Purinergic signaling modulates neurotransmission and neuroinflammation that are involved in behavioral processes and both genetic or acquired neuropathological conditions (Burnstock, 2015).

The purinergic receptors are composed of two subgroups that are expressed throughout the mammalian body: P2 receptors for tri- and diphosphonucleotides such as ATP, ADP, UTP, UDP, and UDP-glucose; and P1 receptors for ADO. The P1 receptors are divided into four subtypes: A_1, A_{2A}, A_{2B}, and A_3. They are metabotropic G protein-coupled receptors linked to activation (A_{2A} and A_{2B}) or inhibition (A_1 and A_3) of adenylyl cyclase (Fredholm et al., 2011; Ralevic and Burnstock, 1998). The P2 receptors are divided into two major subclasses: P2X and P2Y. The P2Y family is also composed of G protein-coupled receptors. Currently, there are eight distinct P2Y subtypes cloned and characterized in mammals: $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_{11}$, $P2Y_{12}$, $P2_{13}$, and $P2Y_{14}$ (Jacobson et al., 2020; Ralevic and Burnstock, 1998). Seven ionotropic receptors form the P2X family (P2X1–P2X7). Among the P2X receptors, the P2X7 receptor is the most involved in inflammatory processes. It plays a crucial role in neuromodulation and neuroinflammation in CNS, together with other purinergic receptors, especially P2X4, $P2Y_6$, $P2Y_{12}$, and A_{2A} (Burnstock, 2015; Illes et al., 2020).

The association between P2X7 receptors stimulation and IL-1β maturation and release was first identified in microglial cells (Ferrari et al., 1996). Currently, the P2X7 receptor is well characterized as the second signal for inflammasome activation that culminates in the cleavage and subsequent release of pro-IL-1β through activation of caspase-1 (Ferrari et al., 2006). The P2X7 receptor induces activation of several microbicidal mechanisms during pathogen infections (Savio et al., 2018; Savio and Coutinho-Silva, 2019), and this receptor is also involved in various brain pathologies, including, among others, Alzheimer’s disease, sepsis-associated encephalopathy, multiple sclerosis, crucial to neuropathic pain, and behavioral conditions such as bipolar disorder and depression (Di Virgilio et al., 2009; Lucae et al., 2006; Parvathenani et al., 2003; Savio et al., 2018; Sharp et al., 2008). The $P2Y_{12}$ receptor mediates the initial microglial migration to injured regions in the CNS (Haynes et al., 2006), while $P2Y_6$ activation by UDP stimulates microglial phagocytosis of dying cells (Koizumi et al., 2007). P2X4 receptor expression in spinal microglia is crucial to pain hypersensitivity after nerve injury (Tsuda et al., 2003). Finally, the A_{2A} receptor in neurons promotes neurodegeneration, while its expression in microglia and astrocytes promotes neuroprotection (Cunha, 2016).

The metabolism of released nucleotides is controlled by ectoenzymes named ectonucleotidases. Of these, the most important ones in the neuroimmune context are E-NTPDase1/CD39, NTPDase2/CD39L1, and NTPDase3/CD39L3 that catalyze the hydrolysis of ATP and ADP to AMP and the ecto-5′-nucleotidase/CD73 that catalyzes the hydrolysis of AMP to adenosine (Table 1). The nucleoside adenosine can be deaminated to inosine by adenosine deaminase (ADA) (Bonan, 2012; Robson et al., 2006). After cortical stab injury, increased hydrolysis of all three adenine nucleotides was specifically observed in the injured cortex. These effects correlate with the upregulation of ectonucleotidases, with CD73 being most highly expressed in astrocytes, whereas CD39 was most highly expressed in microglial cells (Nedeljkovic et al., 2006). CD39 also modulates the migratory activity of microglial cells, as this

Table 1
Expression and functional roles of purinergic receptors, E-NTPDases, and ecto-5′-nucleotidase/CD73 in CNS cells during brain infections.

CNS cell type	Components of purinergic signaling	Expression profile and/or involvement in functional responses in neuroinfections	References
Microglia	P2 receptors: P2X4; P2X7; P2Y4; $P2Y_6$; $P2Y_{12}$; $P2Y_{13}$	HIV: P2X7 induces the production ROS, NO, IL-1β, and TNF-α, resulting in microglial loss.	Chen et al. (2016)
		HSV-1: P2Y12 increase phagocytic function.	Fekete et al. (2018)
		SAE: P2X7 inhibition/deletion decreases microglial activation.	Wang et al. (2015)
	P1 receptors: A_1; A_{2A}; A_{2B}; A_3	TMEV: A_{2A} mediates cannabidiol-induced decreases in microglial activation.	Mecha et al. (2013)
	NTPDase1/CD39; NTPDase2/CD39L1; CD73	HSV-1: Increases CD39 activity.	Fekete et al. (2018)
Astrocytes	P2 receptors: P2X4; P2X7; P2Y1; $P2Y_2$; $P2Y_4$; $P2Y_6$ $P2Y_{12}$; $P2Y_{13}$; $P2Y_{14}$	HIV: P2Y4 induces cytokine and chemokine release.	Zhou et al. (2019)
		HIV: P2X7 is upregulated, inducing neuronal death.	Tewari et al. (2014)
	P1 receptors: A_1; A_{2A}; A_{2B}; A_3	Undefined roles in CNS infections.	
	NTPDase1/CD39; NTPDase2/CD39L1; CD73	*T. gondii*: CD73 promotes tachyzoite-to-bradyzoite differentiation and parasite persistence in the CNS.	Mahamed et al. (2012)
Neurons	P2 receptors: P2X2; P2X4; P2X7*; $P2Y_1$; $P2Y_2$; $P2Y_4$; $P2Y_{12}$; $P2Y_{13}$	SAE: P2X7 deletion decreases neurodegeneration.	Wang et al. (2015)
		HIV: astrocytic P2Y4 induces apoptosis and neuronal death.	Zhou et al. (2019)
		HIV: astrocytic P2X7 contributes to neuronal death	Tewari et al. (2014)
	P1 receptors: A_1; A_{2A}; A_{2B}; A_3	HIV: A1 has neuroprotective effects.	Pingle et al. (2007)
	NTPDase3/CD39L3; CD73	Undefined roles in CNS infections.	

References used for purinergic signaling components expressed by CNS cell types: (Brisevac et al., 2015; Calovi et al., 2019; del Puerto et al., 2013; Grković et al., 2017; Illes et al., 2020; Sheth et al., 2014; Zarrinmayeh and Territo, 2020).

* Ambiguous data reporting P2X7 expression in neurons (Illes et al., 2017).

enzyme controls ATP and adenosine levels, both of which are fundamental molecules to microglial migration (Färber et al., 2008). These ectonucleotidases are involved in several neuropathologies, including, but not limited to epilepsy, Alzheimer's, and Parkinson's disease (Bonan, 2012; Cognato et al., 2011; Lanser et al., 2017; Meng et al., 2019).

Considering the involvement of purinergic receptors and ectonucleotidases in neuroinflammatory and host-pathogen interaction mechanisms, in this review, we discuss advances in the understanding of the role of purinergic signaling in the balance of protective and deleterious inflammatory responses in infectious diseases of CNS.

2. Purinergic signaling in neuroinfectious diseases

2.1. Viral infections

The central nervous system is a major target for viruses that can reach the brain parenchyma and infect neuronal and glial cells. Neuroinfections result in severe neurological complications, including neuroinflammation, encephalitis, neurodegeneration, behavioral changes, and others (McCusker and Kelley, 2013). ATP is released from infected cells in the extracellular milieu where it acts as a danger signal activating surrounding cells that respond by producing inflammatory mediators to control the infection (Savio et al., 2018). Nevertheless, these responses can exacerbate and progress to deleterious consequences. In recent years, several studies have suggested that purinergic signaling is crucial to the outcome of viral infections, influencing both clearance and persistence of the virus in the central nervous system (Ferrari et al., 2018).

The acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV-1), induces neurodegeneration affecting cognitive, motor and, behavioral abilities in almost half of the patients, even with the use of combination antiretroviral therapy (Heaton et al., 2010). HIV-associated dementia is the worst of the HIV-associated neurocognitive disorders. This severe neurological complication is usually found in patients with late-stage AIDS, although it could also be detected early in the development of the disease (Heaton et al., 2010; Nath and Berger, 2004). The HIV transactivator of transcription (Tat) protein and the envelope glycoprotein gp120 act as neurotoxins that stimulate secretion of cytokines such as TNF-α, leading to a dangerous scenario characterized by infected-leukocyte infiltration, inflammation, and neuronal loss (Rappaport et al., 1999; Saha and Pahan, 2003). These processes promote neurocognitive dysfunction that eventually evolves into HIV-dementia.

A typical feature of HIV neuroinfection is neuronal loss (Shi et al., 1996). Tewari and colleagues showed that Tat protein upregulates P2X7 receptor astrocytic expression that results in neuronal death. P2X7 receptor also mediates Tat-induced CCL2 astrocytic release. This chemokine facilitates the infiltration of leukocytes, thereby promoting a pro-inflammatory environment (Tewari et al., 2014). Tat also induces the overexpression of $P2Y_4$ receptor in astrocytes. This purinergic receptor induces cytokine and chemokine release that contributes to apoptosis and neuronal death (Zhou et al., 2019). Furthermore, Tat protein induces monocyte/macrophage infiltration in the CNS, thereby contributing to HIV-dementia development, as this condition is associated with immune cell infiltration (Pu et al., 2003). In this context, A_{2A} receptor activation reduces Tat-induced TNF-α production in HIV-infected monocytes. In addition, A_1 receptor stimulation has protective effects against HIV-1 Tat-induced toxicity in primary cultures of rat cerebellar granule neurons and in rat pheochromocytoma (PC12) cells (Pingle et al., 2007) (Table 1). These findings suggest that adenosine may have a protective role, attenuating the production of pro-inflammatory cytokines by monocytic cells that migrate to CNS (Fotheringham et al., 2004).

The gp120 protein also upregulates the P2X7 receptor in microglial cells. This receptor, in turn, induces the expression of inflammatory mediators such as ROS, NO, IL-1β, and TNF-α, resulting in microglial loss (Chen et al., 2016). Gp120-induced cognitive impairment, including memory and learning deficits, can also occur through P2X7 receptor-dependent mechanisms (Liu et al., 2017). Gp120 also triggers neuropathic pain in HIV patients, a complication displayed in many HIV-neurological disorders (Yuan et al., 2014). This neurotoxin enhances $P2Y_{12}$ receptor expression in glial cells of dorsal root ganglia, activating these cells. Once active, these glial cells increase their expression of pro-inflammatory cytokines such as TNF-α and IL-1β. These are essential cytokines for the development and preservation of thermal and mechanical pain, common features of neuropathic pain (Shi et al., 2018). Taken together, these reports suggest that P2 receptors are deleterious, and P1 receptors are neuroprotective in HIV-dementia. Moreover, such findings support a possible role for ectonucleotidases in this disease, because these enzymes catalyze the hydrolysis of nucleotides to adenosine.

Theiler's murine encephalomyelitis virus (TMEV) infection in susceptible mice strains can persist and develop into a late chronic disease, the symptoms of which include demyelination of white matter, resulting in neurological damage. In humans, multiple sclerosis (MS) is also a demyelinating disease that affects the brain and spinal cord. These findings suggest that TMEV has similarities with multiple sclerosis, including inflammatory cell infiltration, axonal damage, and disruption of the blood–brain barrier (Oleszak et al., 2004). In TMEV disease, the recruitment of leukocytes is a classic step in the development of neuroinflammation. The infection promoted by this cardiovascular virus can be limited by infiltrated leukocytes, including T cells whose activation can be modulated by microglia, preventing neurodegeneration, seizure episodes, and hippocampal injury (Waltl et al., 2018). The anti-inflammatory abilities of cannabidiol attenuate cytokine production and the expression of the vascular cell adhesion molecule-1 (VCAM-1), a pivotal protein in the process of migration of circulating immune cells. These protective effects are partially mediated by the A_{2A} receptor, because the antagonism of this receptor inhibited the beneficial effects of cannabidiol, including the diminished VCAM-1 expression (Mecha et al., 2013).

The herpes simplex virus type 1 (HSV-1) is responsible for more than half of viral encephalitides with clinical manifestations, including seizures, mental impairment, and acute fever (Chen et al., 2019). HSV-1-infected neuronal cells release nucleotides such as ATP that activate and recruit microglia. Then, there is an increase of ectonucleotidase activities (i.e., CD39) to generate more ADP in the extracellular milieu. ADP activates $P2Y_{12}$ receptors in microglia, increasing migration and phagocytic function to clear compromised neurons before cell membrane rupture. This mechanism reduces abnormal neuronal function that could culminate in HSV-1 encephalitis (Fekete et al., 2018). $P2Y_{12}$ receptor is essential for microglial process extension and migration. The $P2Y_{12}$ receptor triggers phosphatidylinositol 3-kinase (PI3K) and phospholipase C (PLC) pathway activation, which generate inositol 1,4,5-triphosphate (PIP3) inducing calcium release from intracellular stores (Illes et al., 2020; Irino et al., 2008). The increase in intracellular Ca^{+2} concentrations is crucial for cytoskeletal reorganization and cell migration. After cell migration, $P2Y_{12}$ receptor downregulation contributes to microglial process retraction. Once microglia cells acquire their ameboid phagocytic phenotype, $P2Y_4$ and $P2Y_6$ receptors control phagocytosis and pinocytosis in these cells, respectively (reviewed in Illes et al., 2020).

Zika virus (ZIKV) is an arbovirus from the Flaviviridae family transmitted mainly by mosquitoes from the *Aedes* genus, including *Aedes aegypti* or *Aedes africanus*. The relationship between ZIKV infection and fetal congenital malformation was first described in Brazil in 2015, when an outbreak of this arbovirus caused severe vertical infection in developing fetuses causing microcephaly and abnormalities in the brain and eyes. In adults, the virus causes meningoencephalitis and Guillain-Barré syndrome, an autoimmune disease that affects the nervous system (Li et al., 2016). The P2X7 receptor appears to be involved in the control of flavivirus as seen in human monocytes infected by dengue virus (DV), a virus closely related to ZIKV. Activation of this receptor reduced viral load in infected cells, mediated by higher levels of ROS and NO production (Corrêa et al., 2016). ZIKV infection activates NLRP3 inflammasome activation and IL-1β secretion (Wang et al., 2018). These findings suggest that the P2X7 receptor may possibly be involved in the pathophysiology of Zika virus infection, and may represent a potential therapeutic target.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) thought to be the causative agent of pandemic coronavirus disease 2019 (COVID-19) (Jin et al., 2020). Patients with more severe outcomes often present with acute respiratory distress syndrome (ARDS). In addition to affecting the respiratory tract, SARS-CoV-2 may present a neuroinvasive profile, and can reach the central nervous system as do other coronaviruses (Wu et al., 2020), possibly through lymphatic vessels (Bostancıklıoğlu, 2020). The ability of this virus to induce neurological symptoms such as headache, acute cerebrovascular diseases, and disturbed consciousness in patients with severe respiratory distress has already been reported (Mao et al., 2020). Furthermore, SARS-CoV-2 may cause patients to become more susceptible to neuroleptic malignant syndrome (NMS), meningoencephalitis, hypogeusia, hyposmia, and even to develop autoimmune disorders that affect neuronal cells, including Guillain-Barré syndrome, regardless of the respiratory condition (Coen et al., 2020; Duong et al., 2020; Kajani et al., 2020; Vavougios, 2020).

The clinical and pathological characteristics presented by SARS-CoV-2 patients may be due to virally-induced cytokine storm, with the hyperinflammation scenario stimulating severe lung disease (Jin et al., 2020). This pulmonary dysfunction can lead to ARDS, which shares various traits with severe pneumonia, the primary complication in hospitalized COVID-19-infected individuals (Jose and Manuel, 2020). Interestingly, ATP-P2X7 receptor signaling mediates LPS-induced ARDS/ALI (acute lung injury) (Cicko et al., 2018; Monção-Ribeiro et al., 2011). Beyond lung epithelial cells, SARS-CoV-2 also presents tropism to macrophages; inhibition of macrophage might prevent coronavirus-related injuries (Fehr and Perlman, 2015). Because the P2X7 receptor is strongly expressed on macrophages and microglia, inducing IL-1β, IL-18 and IL-6 secretion, and because these cells express angiotensin-converting enzyme 2 (ACE2; the receptor used by this virus to infect cells), a recent report introduced the idea that blockade of this purinergic receptor could be a potential target to suppress COVID-19 infection (Virgilio et al., 2020). A recent study found that Anakinra, a human IL-1 receptor antagonist, improved outcomes and decreased mortality among patients with severe forms of COVID-19 (Huet et al., 2020). Taken together, the data suggest that purinergic signaling may be possible involved in the neurological symptoms induced by SARS-CoV-2.

These reports provide evidence for an essential role of purinergic signaling in viral neuroinfectious. Nevertheless, the deleterious or beneficial outcomes depend on the virus species and virulence, as well as the particular purinergic receptor or ectonucleotidase involved in the disease neuropathology. Further studies are needed to better understand purinergic signaling in viral infections, especially in emerging viral infections that affect the central nervous system such as Zika and SARS-CoV-2.

2.2. Bacterial infections

Bacterial infections of the central nervous system are significant causes of morbidity and mortality. These infections are usually associated with encephalitis and meningitis, among the top ten infectious diseases causing death worldwide (Lucas et al., 2016). The most important pathogens that cause these conditions are S. pneumoniae followed by Streptococcus agalactiae, Neisseria meningiditis, Haemophilus influenzae, and Listeria monocytogenes (Cain et al., 2019; Dando et al., 2014). Polymicrobial sepsis is also a severe medical condition that causes neurological symptoms.

High-grade bacteremia and BBB dysfunction are important predisposing factors permitting these pathogens to reach the brain. They invade the CNS through transcellular or paracellular penetration or by infiltrating infected leukocytes, inducing neuroinflammation, excitotoxicity, and neurodegeneration. Interestingly, purinergic signaling is involved in the modulation of these neuropathological mechanisms (Table1) (Dando et al., 2014; Sellner et al., 2010).

Sepsis-associated encephalopathy (SAE) promotes brain dysfunction and is associated exacerbated systemic infection, cytokine release, and immune cell infiltration. In response to this intense inflammatory process, the BBB loses its integrity and protective functions (Nwafor et al., 2019). The P2X7 receptor triggers brain endothelial dysfunction, contributing to SAE pathogenesis. The P2X7 receptor is co-localized with the adhesion molecule ICAM-1, and both of these proteins are highly expressed in cerebral vessels 4 h after sepsis induction by CLP.

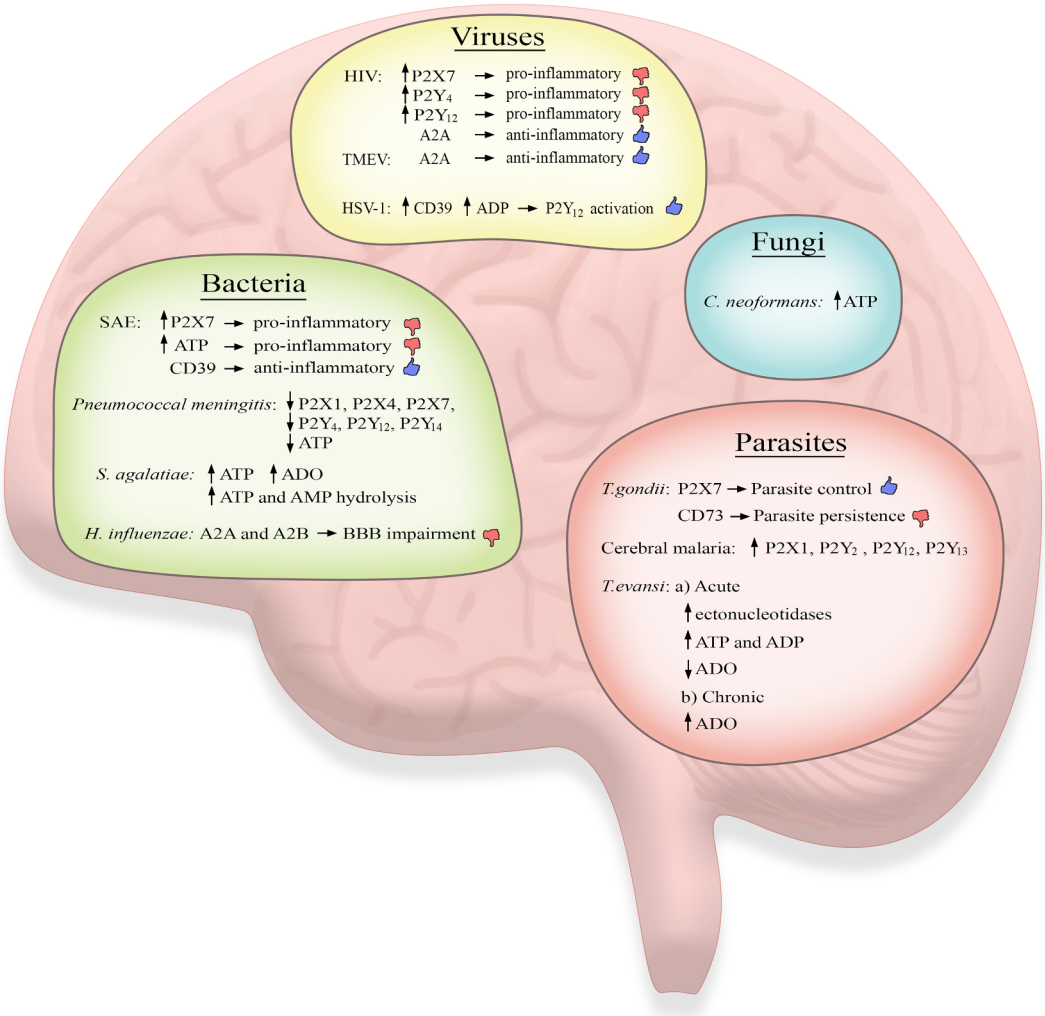

Fig. 1. . Schematic representation of purinergic signaling modulation in infectious diseases that affects the CNS. (A) In human immunodeficiency virus (HIV-1), P2X7, $P2Y_4$, and $P2Y_{12}$ receptors are upregulated and show deleterious pro-inflammatory effects, while A_{2A} has anti-inflammatory activity; In Theiler's murine encephalomyelitis virus (TMEV), A_{2A} also has an anti-inflammatory protective effect; Herpes simplex virus type 1 (HSV-1) infection increases CD39 and ADP levels, boosting microglial $P2Y_{12}$ receptor activation, which in turns increases the phagocytosis of damaged neurons. (B) Sepsis-associated encephalopathy increases ATP concentration and P2X7 receptor expression with deleterious pro-inflammatory effects, while CD39 is protective. Pneumococcal meningitis induces downregulation of cerebral P2X1, P2X4, P2X7, $P2Y_4$, $P2Y_{12}$, $P2Y_{14}$, and ATP levels. *S. agalactiae* infection increases ATP, ADO, and ectonucleotidase activities. In *H. influenzae* infection, A_{2A} and A_{2B} show deleterious effects, inducing BBB impairment. (C) *C. neoformans* infection increases ATP levels in brain tissue. (D) In *T. gondii* infection, the P2X7 receptor has protective effects inducing parasite control, while CD73-generated adenosine contributes to parasite spread and persistence. Cerebral malaria upregulates cerebral expression levels of P2X1, $P2Y_2$, $P2Y_{12}$, and $P2Y_{13}$; *T. evansi* acute infection boosts brain ectonucleotidases, increases ATP and ADP levels, and decreases adenosine brain concentrations. Chronic *T. evansi* increases adenosine brain levels.

Furthermore, leukocyte adhesion, microglial activation, and ICAM-1 expression were decreased when P2X7 signaling was blocked by shRNA or a specific antagonist (A438079). BBB integrity was preserved in $P2X7^{-/-}$ septic mice, demonstrating a critical role for this receptor in SAE (Wang et al., 2015). In the same line of evidence, $P2X7^{-/-}$ septic mice showed decreased ROS and RNS production and increased SOD and CAT activities in cerebral cortex and hippocampus when compared to WT septic animals (Savio et al., 2017). P2X7 receptor genetic deletion also decreased IL-1β and IL-6 production in both brain structures. Furthermore, $CD39^{-/-}$ mice showed increased cytokine production in the brain parenchyma after induction of sepsis, in comparison to WT mice. P2X7 receptor pharmacological blockade inhibited these effects, suggesting that ATP-P2X7 signaling is critical for neuroinflammation in SAE (Savio et al., 2017). In accordance with these findings, Zhang et al. recently showed that ATP concentrations increase in the cerebrospinal fluid of septic mice. Considering that ATP release can occur via pannexin-1 channels, the authors found that blockade of this channel improved cognitive behavior and decreased cytokine production (i.e., IL-1β, IL-6, and TNF-α) in the hippocampus of septic mice (Zhang et al., 2019).

Pneumococcal infections can spread by aerosol and promote asymptomatic colonization of the nasal cavity. Once inside the nasal cavity, these bacteria spread to other organs, including the brain, by reaching the bloodstream and crossing the BBB, causing meningitis (Henriques-normark and Tuomanen, 2013). Some experimental meningitis models have been used to explain the pathogenesis of this disease. Zierhut and colleagues (2017) found that the purinergic signaling could be involved in meningitis. During pneumococcal meningitis, P2 receptor antagonism using suramin and BBG did not change the disease course, despite inhibition of IL-1β and IL-6 secretion in murine bone marrow-derived macrophage (BMDM) challenged by *S. pneumoniae*. The authors also showed that cerebral P2 receptor expression (P2X1, P2X4, P2X7, $P2Y_4$, $P2Y_{12}$ and $P2Y_{14}$) was downregulated and that cerebrospinal fluid ATP concentration decreased in this meningitis model (Zierhut et al., 2017). However, when human THP-1 cells were exposed to the same pathogen, the authors detected

increased ATP levels in the supernatants. Furthermore, pretreatment with a P2X7 antagonist, oxidized ATP (ox-ATP), resulted in reduced IL-1β secretion and attenuated activation of caspase-1 and cathepsin B (Hoegen et al., 2011). *In vivo* and *in vitro* analysis demonstrated that, even using other pathogens such as S. aureus and *Escherichia* coli, ATP was released from host cells. This nucleotide protected against bacterial infections that cause meningitis via the P2X7 receptor and NLRP3 inflammasome activation, cytokine, and chemokine secretion, and by promoting neutrophil recruitment (Xiang et al., 2013).

Several studies reported that other bacteria could trigger the purinergic cascade to promote cerebral inflammation. Silver catfish infected with *S. agalactiae* showed increased brain levels of ATP and adenosine; in this model, IL-1, IL-6, and IL-7 levels increased as well (Souza et al., 2017). Birds infected with *E. coli* presented enhanced ectonucleotidase activities in the cerebral cortex, possibly increasing adenosine formation (da Rosa et al., 2020). Increased adenosine levels could be associated with anti-inflammatory and neuroprotective effects. Neuronal cells, astrocytes, microglia, and pericytes are regulated by adenosine. This molecule, which can be generated by CD73, regulates BBB permeability, neural transmission, and glial cell immune function during stress or injury (Bynoe et al., 2015).

An *in vitro* model that mimics BBB was used to show that *H. influenzae* was able to penetrate endothelial cells, causing an increase in adenosine concentration; furthermore, when A_{2A} and A_{2B} receptors were inhibited, BBB integrity was maintained, suggesting that BBB permeability is modulated by these receptors (Caporarello et al., 2017).

These reports provide evidence that purinergic signaling has an essential role in bacterial infections that cause neurological disorders. In general, ATP-P2 signaling has pro-inflammatory effects. Inhibition of these pathways or adenosine generation improves disease outcomes, decreasing the degree of inflammatory processes, and improving cognitive dysfunction (Fig. 1). Nevertheless, further studies are needed to elucidate the peculiarities of purinergic signaling in each specific infection.

2.3. Fungal infections

The fungus *Cryptococcus neoformans* is the causative agent of cryptococcosis, a disease that can be especially dangerous to immunocompromised hosts, particularly HIV-positive patients. The infection starts with the inhalation of the fungus, followed by dissemination to other organs via the bloodstream. This pathogen exhibits strong tropism for the CNS, leading to a potentially fatal meningoencephalitis (Rajasingham et al., 2017). *C. neoformans* can infect cerebral microvascular endothelial cells from the BBB via a transcellular pathway (Chang et al., 2004). In addition to this mechanism, the pathogen can access the CNS using infected leukocytes such as monocytes and neutrophils (Kaufman-Francis et al., 2018).

Evidence supports the involvement of purinergic signaling in cryptococcosis. The ATP and ADP hydrolysis are reduced in lymphocytes from *C. neoformans*-infected rats, suggesting a reduction of ectonucleotidase activities. These results are possibly connected to the stimulation of a pro-inflammatory scenario with an increase in ATP levels and cytokine production (i.e., TNF-α and INF-γ) (de Azevedo et al., 2014). Indeed, the total ATP concentration increases in the serum and brain tissue during cryptococcosis (de Azevedo et al., 2017). Further studies are needed to elucidate the role of purines and purinergic receptors in the pathophysiology of cryptococcosis.

2.4. Parasitic infections

Toxoplasma gondii is an obligate intracellular protozoan parasite that causes toxoplasmosis. Although the immune response in healthy individuals controls *T. gondii* infection, this parasite can be harmful and potentially fatal to the fetus during pregnancy and to immunocompromised individuals (Schlüter and Barragan, 2019). During acute infection, tachyzoites (the most infectious form) spread throughout almost the entire intestine, lymph nodes, and visceral organs. *T. gondii* can also reach the CNS, where it persists, inducing neurological dysfunction. In the chronic phase, the parasite can transform into bradyzoites and form cysts containing numerous parasites. This fact allows the persistence of the parasite in immunomodulatory sites such as the CNS, inducing neurological and behavioral alterations (Schlüter and Barragan, 2019; Tyebji et al., 2019).

The P2X7 receptor plays a critical role in the immune response against *T. gondii.* This receptor induces parasitic control in macrophages (Corrêa et al., 2010) and human intestinal epithelial cells (Huang et al., 2017) by triggering the activation of microbicidal mechanisms such as ROS production, NLRP3 inflammasome activation, and IL1-β secretion. P2X7-deficient mice are more susceptible to acute and lethal infections caused by type I *T. gondii* (RH) via an impaired immune response (Corrêa et al., 2016). In a model of chronic toxoplasmosis induced by a cystogenic nonvirulent type II *T. gondii* strain (ME-49), P2X7 receptor genetic deletion increased the number of cysts in the mice brain and caused mortality at 6 weeks post-infection, suggesting that this receptor is important for induction of resistance to cerebral toxoplasmosis. Indeed, these knockout mice showed reduced production IL-1β, IL-12, and ROS in the brain, favoring parasite spread in the CNS (Moreira-souza et al., 2019).

In a murine model of congenital toxoplasmosis, investigators isolated telencephalic neuronal progenitor cells from mouse embryos and detected decreased ATP hydrolysis and increased expression of P2X7 receptors in these cells (Bottari et al., 2019). They also found increased expression of the A_{2A} receptor and decreased adenosine deaminase activity, suggesting accumulation of adenosine. Gene expression levels of IL-6, INF-γ, TNF-α, and IL-10 also increased in cells from infected mice. Nevertheless, the parasite load was not assessed in these settings. The authors also found that resveratrol prevented some of these effects. Although they did not investigate the mechanism of action of resveratrol, these results may be related to its antioxidant and anti-inflammatory activities (Bottari et al., 2019).

Tonin and colleagues (2014) measured levels of purines in the brains of rats infected with two *T. gondii* strains (RH and ME-49). The levels of purines (ATP, ADP, AMP, adenosine, inosine, xanthine, and hypoxanthine) increased in the brains of rats infected with the RH strain at 4- and 6-days post-infection. By contrast, purine levels significantly decreased in the brains of rats infected with type II cystogenic *T. gondii* strain (ME-49) 60 days post-infection. ADA activity decreased 30 days post-infection but increased 60 days post-infection in the brains of rats infected with the ME-49 strain. Taken together, these data suggest that purine concentrations and ADA activity in the brain can vary during disease evolution, and may depend on the *T. gondii* strain (Tonin et al., 2014).

In addition to ADA inhibition, CD73-generated adenosine can contribute to the pathogenesis of cerebral toxoplasmosis. CD73-deficient mice are less susceptible to cystogenic *T. gondii* (ME-49) infection than are WT animals. CD73 expression increases in the brain throughout the infection. $CD73^{-/-}$ animals showed a significant reduction in parasitic load during the chronic phase when compared to the WT group. Furthermore, CD73 induced tachyzoite-to-bradyzoite differentiation in glial cells, suggesting that adenosine generation by host cells contributes to cyst formation and infection persistence in the CNS (Mahamed et al., 2012). These reports suggest a crucial role for purinergic signaling in cerebral toxoplasmosis. The P2X7 receptor participates in the activation of microbicidal mechanisms and parasite control, while adenosine generation favors the persistence of the parasite in the CNS.

Malaria is an infectious disease caused by parasites of the genus *Plasmodium*. This disease is transmitted by female *Anopheles* mosquitoes that inject sporozoites into the host, and infected patients can have moderate-to-severe malaria, characterized by anemia, fever, and, in some cases, cerebral manifestations (Luzolo and Ngoyi, 2019).

Plasmodium falciparum is responsible for the most significant number of malaria cases worldwide. Cerebral malaria is a critical clinical complication of *P. falciparum* infection, characterized by neuroinflammation, seizures, unconsciousness, coma, and diffuse encephalopathy (Luzolo and Ngoyi, 2019).

Purinergic signaling is involved in malaria pathophysiology because *Plasmodium*-infected erythrocytes release large amounts of ATP, and the P2X7 receptor is critical for a beneficial Th1 immune response to this disease (Akkaya et al., 2009; de Salles et al., 2017). In a murine model of cerebral malaria, the expression of purinergic receptors varied according to receptor subtype and brain region studied. P2X1 and $P2Y_2$ expression increased in the olfactory bulb, prefrontal cortex, and hippocampus, while $P2Y_{12}$ and $P2Y_{13}$ expression increased in the cerebellum (Marín-García et al., 2009). Nevertheless, further studies are required to determine the functional role of these receptors in cerebral malaria.

Trypanosoma evansi is a protozoan that causes neurological dysfunction in several mammals (Habila et al., 2012). In humans, the first case of *T. evansi* infection was reported in India. The infected individual presented with sensory deficit, disorientation, and violent behavior (Joshi et al., 2005). In the context of purinergic signaling, Oliveira and colleagues (2011) detected increased ATP, ADP, and AMP hydrolysis in synaptosomes isolated from the cerebral cortex of *T. evansi*-infected rats 5 days post-infection, while ADA activity was reduced in these settings (Da et al., 2011). These results suggest an accumulation of adenosine in the cerebral cortex of infected rats; however, another study from the same group found increased ATP and ADP levels and decreased ADO concentrations in this brain region 5 days after *T. evansi* infection (Da et al., 2012). During the chronic phase, increased levels of adenosine were detected in the brain *T. evansi*-infected rats, possibly favoring neuroprotection and neuromodulatory mechanisms during the infection (Da et al., 2012).

2.5. Targeting purinergic signaling in neuroinfectious diseases

Given the important role of purinergic signaling in infectious diseases of the CNS, therapeutic approaches targeting this signaling would represent feasible strategies to treat these diseases and their associated neurological symptoms. Brain-penetrant purinergic receptor agonists and antagonists, as well as ectonucleotidases inhibitors, have been tested in preclinical or clinical studies, as detailed in recent reviews (Allard et al., 2017; Bhattacharya, 2018; Effendi et al., 2020; Savio et al., 2018; Zarrinmayeh and Territo, 2020). In this section, we discuss some examples of drugs that could modulate purinergic signaling in neuroinfections.

P2X7, P2X4, and P2X3 are the most relevant P2X receptors from a neuropharmacological perspective. The availability of brain-permeable P2X7 inhibitors is limited. BBG and A438079 are P2X7 antagonists that efficiently cross the blood–brain barrier. BBG is most commonly used in animal models of neurological diseases, while the use of A438079 is less attractive because of its unfavorable pharmacokinetic proprieties (Savio et al., 2018). JNJ-554175446 and JNJ-55308942 are promising brain-penetrant P2X7 receptor antagonists that have been evaluated in clinical trials for treatment of neuropathologies (Bhattacharya, 2018). P2X4 receptor inhibition has also been proposed to treat these diseases. However, most of the drugs described for this receptor are allosteric ligands with low potency and poor aqueous solubility (i.e., 5-BDBD and BX-430). The most exciting P2X4 antagonist to control pain by acting in glial cells is the NC-2600, which is currently in a phase II clinical trial (Zarrinmayeh and Territo, 2020). Furthermore, A-317491, a selective and competitive antagonist for both homomeric P2X3 and heteromeric P2X2/P2X3 receptors, attenuates tactile allodynia and thermal hyperalgesia in a classic neuropathic pain model (Jarvis et al., 2002).

P2Y receptor ligands have also been studied for neuroprotective purposes. $P2Y_2$ and $P2Y_4$ receptors may have complementary effects by activating microglial phagocytosis and pinocytosis of soluble amyloid β protein fragments in Alzheimer's disease (Weisman et al., 2012). Diquafosol (INS365), a $P2Y_2$ agonist, has already been approved as a topical treatment for dry-eye disease (Yamane et al., 2015), and two additional agonists are in clinical trials (INS37217 and MRS2698) (Zarrinmayeh and Territo, 2020). $P2Y_1$ inhibition attenuates cognitive dysfunction after brain injury (Guzman and Gerevich, 2016). The activation of $P2Y_1$ by the agonist MRS2365 boosts inflammatory responses and increases the infarct volume in a stroke model, while the antagonist MRS2179 show opposite protective effects after cerebral ischemia (Förster and Reiser, 2015; Kuboyama et al., 2011). $P2Y_6$ antagonist MRS2578 reduces inflammatory neurodegeneration, while the agonist MRS-2693 induces microglia activation and neuronal loss (Neher et al., 2014). $P2Y_{12}$ receptor is also an exciting target for neuroinflammatory diseases by control microglia migration and process extension. Initially developed to restrain platelet aggregation, $P2Y_{12}$ antagonists are commercially available, including ticlopidine (Ticlid), clopidogrel (Plavix), ticagrelor (Brilinta), prasugrel (Effient), and ticagrelor (AR-C69931) (Bhatt et al., 2013; Webster et al., 2013).

The P1 receptors are also therapeutic targets for CNS diseases. A_1 and A_{2A} receptors are the central adenosine receptors expressed in the brain, and they usually have contrasting effects. The A_1 receptor has neuroprotective activities, while A_{2A} receptor is considered a neurodegenerative receptor (Stockwell et al., 2017). The development of A_1 agonists and A_{2A} antagonists could then have beneficial effects on neurological disorders (Cieślak and Wojtczak, 2018). Although most adenosine receptor drugs are unable to cross the BBB, MMPD and MRS5474 can act as brain A_1 agonists, and MRS5474 showed antidepressant properties (Jacobson et al., 2019). Furthermore, A_{2A} antagonists such as istradefylline and SCH58261 can inhibit microglial activation and excitotoxicity (Zarrinmayeh and Territo, 2020). Other adenosine receptor drugs in CNS diseases have been extensively reviewed in Effendi et al. (Effendi et al., 2020).

Finally, ectonucleotidase inhibitors could be used for modulating the extracellular availability of nucleotides and nucleosides and, consequently, the activation of purinergic receptors during brain infections. Sodium polyoxotungstate (POM-1) and ARL6715 are the primary NTPDase/CD39 inhibitors that have been used to increase ATP availability, whereas soluble apyrase has been used to scavenge ATP (Allard et al., 2017; Bonan, 2012) APCP (α, β-methyleneadenosine 5′-diphosphate monosodium salt) is the main inhibitor of CD73 limiting adenosine generation (Bonan, 2012). In addition to these drugs, CD39/CD73-neutralizing antibodies are also feasible therapeutic strategies for modulating purinergic signaling (Allard et al., 2017).

3. Concluding remarks

The immune and nervous systems are actively integrated and they modulate several physiological and pathological mechanisms. An understanding of the integrated mechanisms of these two physiological systems is fundamental for the development of new therapeutic strategies for infectious diseases that affect the central nervous system.

Purinergic signaling is an evolutionarily well-conserved signaling pathway that modulates immune and neural responses, serving as a communication link between these two systems. In general, ATP-P2 receptor signaling has pro-inflammatory and deleterious effects, aggravating viral infections that affect the CNS, while adenosine appears to have anti-inflammatory and protective effects. In bacterial infections, ATP signaling appears to have beneficial effects on cells of the immune system, inducing infection control. However, in cerebral parenchymal cells, this signaling has deleterious effects, promoting neuroinflammation, excitotoxicity, and neurodegeneration. By contrast, the activation of P2 receptors, mainly the P2X7 receptor, appears to be crucial for control parasitic infections by inducing the activation of microbicidal mechanisms. Adenosine signaling in parasitic infections appears to favor the parasite persistence in the CNS, as in cerebral toxoplasmosis (Fig. 1). Taken together, the data suggest that deleterious or beneficial

outcomes depend on the pathogen species and its virulence, as well as the particular component of purinergic signaling involved in the neuroinfectious disease.

An understanding of purinergic signaling in infectious diseases that affect the CNS may suggest new therapeutic strategies, for example, the administration of purinergic receptor agonists/antagonists and soluble apyrases that mimic the action of ectonucleotidases. Furthermore, the administration of CD39 neutralizing antibodies is an exciting alternative in cases where ATP signaling is important for infection control.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by funds from the Conselho Nacional de Desenvolvimento Cientifico e Tecnológico do Brasil – CNPq (306839/2019-9 to RCS), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro - FAPERJ (E-26/202.701/2019 and E-26/010.002260/2019 to LEBS; 26/010.101036/2018 and E-26/202.774/2018 to RCS).

References

Weisman, A.G., Woods, T., Erb, L., Seye, I.C., 2012. P2Y Receptors in the mammalian nervous system: pharmacology, ligands and therapeutic potential. CNS & Neurol. Disorders – Drug Targets. https://doi.org/10.2174/187152712803581047.

Akkaya, C., Shumilina, E., Bobballa, D., Brand, V.B., Mahmud, H., Lang, F., Huber, S.M., 2009. The Plasmodium falciparum-induced anion channel of human erythrocytes is an ATP-release pathway. Pflugers Arch. Eur. J. Physiol. 457, 1035–1047. https://doi.org/10.1007/s00424-008-0572-8.

Allard, B., Longhi, M.S., Robson, S.C., Stagg, J., 2017. The ectonucleotidases CD39 and CD73: Novel checkpoint inhibitor targets. Immunol. Rev. 276, 121–144. https://doi.org/10.1111/imr.12528.

de Azevedo, M.I., Ferreiro, L., Da Silva, A.S., Tonin, A.A., Ruchel, J.B., Rezer, J.F.P., França, R.T., Zimmermann, C.E.P., Leal, D.B.R., Duarte, M.M.M.F., Lopes, S.T.A., Flores, M.M., Fighera, R., Santurio, J.M., 2014. E-NTPDase and E-ADA activities in rats experimental infected by Cryptococcus neoformans. Vet. Microbiol. 174, 206–213. https://doi.org/10.1016/j.vetmic.2014.09.007.

Bhatt, D.L., Stone, G.W., Mahaffey, K.W., Gibson, C.M., Steg, P.G., Hamm, C.W., Price, M.J., Leonardi, S., Gallup, D., Bramucci, E., Radke, P.W., Widimský, P., Tousek, F., Tauth, J., Spriggs, D., McLaurin, B.T., Angiolillo, D.J., Généreux, P., Liu, T., Prats, J., Todd, M., Skerjanec, S., White, H.D., Harrington, R.A., 2013. Effect of platelet inhibition with Cangrelor during PCI on ischemic events. N. Engl. J. Med. 368, 1303–1313. https://doi.org/10.1056/NEJMoa1300815.

Bhattacharya, A., 2018. Recent advances in CNS P2X7 physiology and pharmacology: focus on neuropsychiatric disorders. Front. Pharmacol. 9, 1–7. https://doi.org/10.3389/fphar.2018.00030.

Bonan, C.D., 2012. Ectonucleotidases and nucleotide/nucleoside transporters as pharmacological targets for neurological disorders. CNS Neurol. Disord. – Drug Targets 11, 739–750. https://doi.org/10.2174/187152712803581092.

Bostancıklıoğlu, M., 2020. SARS-CoV2 entry and spread in the lymphatic drainage system of the brain. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2020.04.080.

Bottari, N.B., Pillat, M.M., Schetinger, M.R.C., et al., 2019. Resveratrol-mediated reversal of changes in purinergic signaling and immune response induced by Toxoplasma gondii infection of neural progenitor cells. Purinergic Signal 15 (1), 77–84. https://doi.org/10.1007/s11302-018-9634-3.

Brisevac, D., Adzic, M., Laketa, D., Parabucki, A., Milosevic, M., Lavrnja, I., Bjelobaba, I., Sévigny, J., Kipp, M., Nedeljkovic, N., 2015. Extracellular ATP selectively upregulates ecto-nucleoside triphosphate diphosphohydrolase 2 and ecto-5′-nucleotidase by rat cortical astrocytes in Vitro. J. Mol. Neurosci. 57, 452–462. https://doi.org/10.1007/s12031-015-0601-y.

Bruzzone, R., Dubois-Dalcq, M., Grau, G.E., Griffin, D.E., Kristensson, K., 2009. Infectious diseases of the nervous system and their impact in developing countries. PLoS Pathog. 5, 5–7. https://doi.org/10.1371/journal.ppat.1000199.

Burnstock, G., 2015. An introduction to the roles of purinergic signalling in neurodegeneration, neuroprotection and neuroregeneration. Neuropharmacology 104, 4–17. https://doi.org/10.1016/j.neuropharm.2015.05.031.

Burnstock, G., 1972. Purinergic nerves. Pharmacol. Rev. 24, 509–581.

Burnstock, G., Campbell, G., Satchell, D., Smythe, A., 1970. Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. Br. J. Pharmacol. 40, 668–688. https://doi.org/10.1111/j.1476-5381.1970.tb10646.x.

Burnstock, G., Verkhratsky, A., 2009. Evolutionary origins of the purinergic signalling system. Acta Physiol. 195, 415–447. https://doi.org/10.1111/j.1748-1716.2009.01957.x.

Bynoe, M.S., Viret, C., Yan, A., Kim, D.G., 2015. Adenosine receptor signaling: A key to opening the blood-brain door. Fluids Barriers CNS 12, 1–12. https://doi.org/10.1186/s12987-015-0017-7.

Cain, M.D., Salimi, H., Diamond, M.S., Klein, R.S., 2019. Mechanisms of Pathogen Invasion into the Central Nervous System. Neuron 103, 771–783. https://doi.org/10.1016/j.neuron.2019.07.015.

Calovi, S., Mut-Arbona, P., Sperlágh, B., 2019. Microglia and the purinergic signaling system. Neuroscience 405, 137–147. https://doi.org/10.1016/j.neuroscience.2018.12.021.

Caporarello, N., Olivieri, M., Cristaldi, M., Scalia, M., Toscano, M.A., Genovese, C., Addamo, A., Salmeri, M., Lupo, G., Anfuso, C.D., 2017. Blood-brain barrier in a haemophilus influenzae type a in vitro infection: role of adenosine receptors A2A and A2B. Mol. Neurobiol. 55, 5321–5336. https://doi.org/10.1007/s12035-017-0769-y.

Carson, M.J., Doose, J.M., Melchior, B., Schmid, C.D., Ploix, C.C., 2006. CNS immune privilege: Hiding in plain sight. Immunol. Rev. 213, 48–65. https://doi.org/10.1111/j.1600-065X.2006.00441.x.

Chang, Y.C., Stins, M.F., Mccaffery, M.J., Miller, G.F., Pare, D.R., Dam, T., Paul-satyasee, M., Kim, K.S., Kwon-chung, K.J., Mmun, I.N.I., 2004. Cryptococcal yeast cells invade the central nervous system via transcellular penetration of the blood-brain barrier. Infect. Immun. 72, 4985–4995. https://doi.org/10.1128/IAI.72.9.4985.

Chen, Q., Wu, H., Qin, S., Liu, C., Chen, Y., Yang, Y., Xu, C., 2016. The P2X7 receptor involved in gp120-induced cell injury in BV2 microglia. Inflammation 39, 1814–1826. https://doi.org/10.1007/s10753-016-0417-0.

Chen, Z., Zhong, D., Li, G., 2019. The role of microglia in viral encephalitis: a review. J. Neuroinflamm. 16, 1–12. https://doi.org/10.1186/s12974-019-1443-2.

Cicko, S., Köhler, T.C., Ayata, C.K., Müller, T., Ehrat, N., Meyer, A., Hossfeld, M., Zech, A., Di Virgilio, F., Idzko, M., 2018. Extracellular ATP is a danger signal activating P2X7 Receptor in a LPS mediated inflammation (ARDS/ALI). Oncotarget 9, 30635–30648. https://doi.org/10.18632/oncotarget.25761.

Cieślak, M., Wojtczak, A., 2018. Role of purinergic receptors in the Alzheimer's disease. Purinergic Signal. 14, 331–344. https://doi.org/10.1007/s11302-018-9629-0.

Cisneros-Mejorado, A., Pérez-Samartín, A., Gottlieb, M., Matute, C., 2014. ATP signaling in brain: release, excitotoxicity and potential therapeutic targets. Cell. Mol. Neurobiol. 35, 1–6. https://doi.org/10.1007/s10571-014-0092-3.

Coen, M., Jeanson, G., Culebras Almeida, L.A., Hübers, A., Stierlin, F., Najjar, I., Ongaro, M., Moulin, K., Makrygianni, M., Leemann, B., Kronig, I., Bertrand, J., Reny, J.-L., Schibler, M., Serratrice, J., 2020. Guillain-Barré syndrome as a complication of SARS-CoV-2 infection. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2020.04.074.

Cognato, G.P., Vuaden, F.C., Savio, L.E.B., Bellaver, B., Casali, E., Bogo, M.R., Souza, D.O.G., Sévigny, J., Bonan, C.D., 2011. Nucleoside triphosphate diphosphohydrolases role in the pathophysiology of cognitive impairment induced by seizure in early age. Neuroscience 180, 191–200. https://doi.org/10.1016/j.neuroscience.2011.01.065.

Corrêa, G., Almeida Lindenberg, C.D., Moreira-Souza, A.C.D.A., Savio, L.E.B., Takiya, C.M., Marques-da-Silva, C., Vommaro, R.C., Coutinho-Silva, R., 2016. Inflammatory early events associated to the role of P2X7 receptor in acute murine toxoplasmosis. Immunobiology. https://doi.org/10.1016/j.imbio.2016.12.007.

Corrêa, Gladys, de A. Lindenberg, C., Fernandes-Santos, C., Gandini, M., Petitinga Paiva, F., Coutinho-Silva, R., F. Kubelka, C., 2016. The purinergic receptor P2X7 role in control of Dengue virus-2 infection and cytokine/chemokine production in infected human monocytes. Immunobiology 221, 794–802. https://doi.org/10.1016/j.imbio.2016.02.003.

Corrêa, G., Marques da Silva, C., de Abreu Moreira-Souza, A.C., Vommaro, R.C., Coutinho-Silva, R., 2010. Activation of the P2X7 receptor triggers the elimination of Toxoplasma gondii tachyzoites from infected macrophages. Microbes Infect. 12, 497–504. https://doi.org/10.1016/j.micinf.2010.03.004.

Cunha, R.A., 2016. How does adenosine control neuronal dysfunction and neurodegeneration? J. Neurochem. 139, 1019–1055. https://doi.org/10.1111/jnc.13724.

Da, A.S., Bellé, L.P., Bitencourt, P.E.R., Garcia, H.A., Thomé, G.R., Costa, M.M., Oliveira, C.B., Teixeira, M.M.G., Moretto, M.B., Mazzanti, C.M., Lopes, S.T.A., Monteiro, S.G., 2011. Experimental Parasitology Trypanosoma evansi: adenosine deaminase activity in the brain of infected rats. Exp. Parasitol. 127, 173–177. https://doi.org/10.1016/j.exppara.2010.07.010.

Da, A.S., Oliveira, C.B., Rosa, L.D., Leal, C.A.M., Da, R.C., Thomé, G.R., Athayde, M.L., Schetinger, M.R.C., Monteiro, S.G., Lopes, S.T.A., 2012. Experimental Parasitology Influence of Trypanosoma evansi in adenine nucleotides and nucleoside concentration in serum and cerebral cortex of infected rats. Exp. Parasitol. 131, 80–84. https://doi.org/10.1016/j.exppara.2012.03.008.

da Rosa, G., Alba, D.F., Silva, A.D., Miron, V.V., Morsch, V.M., Boiago, M.M., Stefani, L.M., Baldissera, M.M., Lopes, M.T., Mendes, R.E., da Silva, A.S., 2020. Impacts of Escherichia coli infection in young breeder chicks on the animal behavior and cerebral activity of purinergic and cholinergic enzymes involved in the regulation of molecules with neurotransmitter and neuromodulator function. Microb. Pathog. 138, 103787. https://doi.org/10.1016/j.micpath.2019.103787.

Dando, S.J., Mackay-Sim, A., Norton, R., Currie, B.J., St. John, J.A., Ekberg, J.A.K., Batzloff, M., Ulett, G.C., Beacham, I.R., 2014. Pathogens penetrating the central nervous system: Infection pathways and the cellular and molecular mechanisms of invasion. Clin. Microbiol. Rev. 27, 691–726. https://doi.org/10.1128/CMR.00118-13.

Daneman, Ri, Prat, A., 2015. The blood-brain barrier. Cold Spring Harb. Lab. Press 7, 1–23. https://doi.org/10.1111/j.1469-8749.1961.tb10410.x.

Daniel, M., Danielová, V., Fialová, A., Malý, M., Kříž, B., Nuttall, P.A., 2018. Increased relative risk of tick-borne encephalitis in warmer weather. Front. Cell. Infect. Microbiol. 8, 1–11. https://doi.org/10.3389/fcimb.2018.00090.

de Azevedo, M.I., Da Silva, A.S., Ferreiro, L., Doleski, P.H., Tonin, A.A., Casali, E.A.,

Moritz, C.E.J., Schirmbeck, G.H., Cardoso, V.V., Flores, M.M., Fighera, R., Santurio, J.M., 2017. Serum and brain purine levels in an experimental systemic infection of mice by Cryptococcus neoformans: purinergic immunomodulatory effects. Microb. Pathog. 113, 124–128. https://doi.org/10.1016/j.micpath.2017.10.012.
del Puerto, A., Wandosell, F., Garrido, J.J., 2013. Neuronal and glial purinergic receptors functions in neuron development and brain disease. Front. Cell. Neurosci. 7, 1–15. https://doi.org/10.3389/fncel.2013.00197.
Di Virgilio, F., Ceruti, S., Bramanti, P., Abbracchio, M.P., 2009. Purinergic signalling in inflammation of the central nervous system. Trends Neurosci. 32, 79–87. https://doi.org/10.1016/j.tins.2008.11.003.
Drury, A.N., Szent-Gyorgyi, A., 1929. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J. Physiol. 68, 213–237.
Duong, L., Xu, P., Liu, A., 2020. Meningoencephalitis without respiratory failure in a young female patient with COVID-19 infection in Downtown Los Angeles, early April 2020. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2020.04.024.
Effendi, W.I., Nagano, T., Kobayashi, K., Nishimura, Y., 2020. Focusing on adenosine receptors as a potential targeted therapy in human diseases. Cells 9, 785. https://doi.org/10.3390/cells9030785.
Engelhardt, B., Vajkoczy, P., Weller, R.O., 2017. The movers and shapers in immune privilege of the CNS. Nat. Immunol. 18, 123–131. https://doi.org/10.1038/ni.3666.
Färber, K., Markworth, S., Pannasch, U., Nolte, C., Prinz, Vi, Kronenberg, G., Gertz, K., Endres, M., Bechmann, I., Enjyoji, K., Robson, S.C., Kettenmann, H., 2008. The ectonucleotidase cd39/ENTPDase1 modulates purinergic-mediated microglial migration. Wiley-Liss 56, 331–341. https://doi.org/10.1002/glia.
Fehr, A.R., Perlman, S., 2015. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses Methods Protoc. 1282, 1–282. https://doi.org/10.1007/978-1-4939-2438-7.
Fekete, R., Cserép, C., Lénárt, N., Tóth, K., Orsolits, B., Martinecz, B., Méhes, E., Szabó, B., Németh, V., Gönci, B., Sperlágh, B., Boldogkői, Z., Kittel, Á., Baranyi, M., Ferenczi, S., Kovács, K., Szalay, G., Rózsa, B., Webb, C., Kovacs, G.G., Hortobágyi, T., West, B.L., Környei, Z., Dénes, Á., 2018. Microglia control the spread of neurotropic virus infection via P2Y12 signalling and recruit monocytes through P2Y12-independent mechanisms. Acta Neuropathol. 136, 461–482. https://doi.org/10.1007/s00401-018-1885-0.
Ferrari, D., Idzko, M., Müller, T., Manservigi, R., Marconi, P., 2018. Purinergic signaling: a new pharmacological target against viruses? Trends Pharmacol.Sci. 39, 926–936. https://doi.org/10.1016/j.tips.2018.09.004.
Ferrari, D., Pizzirani, C., Adinolfi, E., Lemoli, R.M., Curti, A., Idzko, M., Panther, E., Di Virgilio, F., 2006. The P2X7 Receptor: a key player in IL-1 processing and release. J. Immunol. 176, 3877–3883. https://doi.org/10.4049/jimmunol.176.7.3877.
Ferrari, D., Villalba, M., Chiozzi, P., Falzoni, S., Ricciardi-Castagnoli, P., Di Virgilio, F., 1996. Mouse microglial cells express a plasma membrane pore gated by extracellular ATP. J. Immunol. 156, 1531–1539.
Förster, D., Reiser, G., 2015. Supportive or detrimental roles of P2Y receptors in brain pathology?—The two faces of P2Y receptors in stroke and neurodegeneration detected in neural cell and in animal model studies. Purinergic Signal. 11, 441–454. https://doi.org/10.1007/s11302-015-9471-6.
Fotheringham, J., Mayne, M., Holden, C., Nath, A., Geiger, J.D., 2004. Adenosine receptors control HIV-1 Tat-induced inflammatory responses through protein phosphatase. Virology 327, 186–195. https://doi.org/10.1016/j.virol.2004.07.007.
Fredholm, B.B., IJzerman, A.P., Jacobson, K.A., Linden, J., Müller, C.E., 2011. International union of basic and clinical pharmacology. LXXXI. Nomenclature and classification of adenosine receptors – an update. Pharmacol. Rev. 63, 1–34. https://doi.org/10.1124/pr.110.003285.
Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., Mehler, M.F., Conway, S.J., Ng, L.G., Stanley, E.R., Samokhvalov, I.M., Merad, M., 2010. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science (80-.) 330, 841–845. https://doi.org/10.1126/science.1194637.
Grković, I., Drakulić, D., Martinović, J., Mitrović, N., 2017. Role of ectonucleotidases in synapse formation during brain development: physiological and pathological implications. Curr. Neuropharmacol. 17, 84–98. https://doi.org/10.2174/1570159x15666170518151541.
Guzman, S.J., Gerevich, Z., 2016. P2Y receptors in synaptic transmission and plasticity: therapeutic potential in cognitive dysfunction. Neural Plast. 2016. https://doi.org/10.1155/2016/1207393.
Habila, N., Inuwa, M.H., Aimola, I.A., Udeh, M.U., Haruna, E., 2012. Pathogenic mechanisms of Trypanosoma evansi infections. Res. Vet. Sci. 93, 13–17. https://doi.org/10.1016/j.rvsc.2011.08.011.
Haroon, E., Miller, A.H., Sanacora, G., 2017. Inflammation, glutamate, and glia: a trio of trouble in mood disorders. Neuropsychopharmacology 42, 193–215. https://doi.org/10.1038/npp.2016.199.
Haynes, S.E., Hollopeter, G., Yang, G., Kurpius, D., Dailey, M.E., Gan, W.B., Julius, D., 2006. The P2Y12 receptor regulates microglial activation by extracellular nucleotides. Nat. Neurosci. 9, 1512–1519. https://doi.org/10.1038/nn1805.
Heaton, R.K., Clifford, D.B., Franklin, D.R., Woods, S.P., Ake, C., Vaida, F., Ellis, R.J., Letendre, S.L., Marcotte, T.D., Atkinson, J.H., Rivera-Mindt, M., Vigil, O.R., Taylor, M.J., Collier, A.C., Marra, C.M., Gelman, B.B., McArthur, J.C., Morgello, S., Simpson, D.M., McCutchan, J.A., Abramson, I., Gamst, A., Fennema-Notestine, C., Jernigan, T.L., Wong, J., Grant, I., 2010. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy. Neurology 75, 2087–2096. https://doi.org/10.1212/WNL.0b013e318200d727.
Henriques-normark, B., Tuomanen, E.I., 2013. The pneumococcus: epidemiology, microbiology, and pathogenesis. Cold Spring Harb. Perspect. Med. 3, 1–16.
Hoegen, T., Tremel, N., Klein, M., Angele, B., Wagner, H., Kirschning, C., Pfister, H.-W., Fontana, A., Hammerschmidt, S., Koedel, U., 2011. The NLRP3 inflammasome contributes to brain injury in pneumococcal meningitis and is activated through ATP-dependent lysosomal cathepsin B release. J. Immunol. 187, 5440–5451. https://doi.org/10.4049/jimmunol.1100790.
Huang, S.W., Walker, C., Pennock, J., Else, K., Muller, W., Daniels, M.J., Pellegrini, C., Brough, D., Lopez-Castejon, G., Cruickshank, S.M., 2017. P2X7 receptor-dependent tuning of gut epithelial responses to infection. Immunol. Cell Biol. 95, 178–188. https://doi.org/10.1038/icb.2016.75.
Huet, T., Beaussier, H., Voisin, O., Jouveshomme, S., Dauriat, G., Lazareth, I., Sacco, E., Naccache, J.M., Bézie, Y., Laplanche, S., Le Berre, A., Le Pavec, J., Salmeron, S., Emmerich, J., Mourad, J.J., Chatellier, G., Hayem, G., 2020. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 393–400. https://doi.org/10.1016/S2665-9913(20)30164-8.
Illes, P., Khan, T.M., Rubini, P., 2017. Neuronal P2X7 receptors revisited: Do they really exist? J. Neurosci. 37, 7049–7062. https://doi.org/10.1523/JNEUROSCI.3103-16.2017.
Illes, P., Rubini, P., Ulrich, H., Zhao, Y., Tang, Y., 2020. Regulation of microglial functions by purinergic mechanisms in the healthy and diseased CNS. Cells 9, 1–24. https://doi.org/10.3390/cells9051108.
Irino, Y., Nakamura, Y., Inoue, K., Kohsaka, S., Ohsawa, K., 2008. Akt activation is involved in P2Y12 receptor-mediated chemotaxis of microglia. J. Neurosci. Res. 86, 1511–1519. https://doi.org/10.1002/jnr.21610.
Jacobson, K.A., Delicado, E.G., Gachet, C., Kennedy, C., von Kügelgen, I., Li, B., Miras-Portugal, M.T., Novak, I., Schöneberg, T., Perez-Sen, R., Thor, D., Wu, B., Yang, Z., Müller, C.E., 2020. Update of P2Y receptor pharmacology: IUPHAR Review 27. Br. J. Pharmacol. 0–2. https://doi.org/10.1111/bph.15005.
Jacobson, K.A., Tosh, D.K., Jain, S., Gao, Z.G., 2019. Historical and current adenosine receptor agonists in preclinical and clinical development. Front. Cell. Neurosci. 13, 1–17. https://doi.org/10.3389/fncel.2019.00124.
Jarvis, M.F., Burgard, E.C., McGaraughty, S., Honore, P., Lynch, K., Brennan, T.J., Subieta, A., Van Biesen, T., Cartmell, J., Bianchi, B., Niforatos, W., Kage, K., Yu, H., Mikusa, J., Wismer, C.T., Zhu, C.Z., Chu, K., Lee, C.H., Stewart, A.O., Polakowski, J., Cox, B.F., Kowaluk, E., Williams, M., Sullivan, J., Faltynek, C., 2002. A-317491, a novel potent and selective non-nucleotide antagonist of P2X3 and P2X2/3 receptors, reduces chronic inflammatory and neuropathic pain in the rat. Proc. Natl. Acad. Sci. USA 99, 17179–17184. https://doi.org/10.1073/pnas.252537299.
Jin, Y., Yang, H., Ji, W., Che, S., Zhang, W., Duan, G., 2020. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 372, 1–17.
Jose, R.J., Manuel, A., 2020. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir. Med. 2019, 2019–2020. https://doi.org/10.1016/S2213-2600(20)30216-2.
Joshi, P.P., Shegokar, V.R., Powar, R.M., Herder, S., Katti, R., Salkar, H.R., Dani, V.S., Bhargava, A., Jannin, J., Truc, P., 2005. Human trypanosomiasis caused by Trypanosoma evansi in India: the first case report. Am. J. Trop. Med. Hyg. 73, 491–495. https://doi.org/10.4269/ajtmh.2005.73.491.
Kajani, R., Apramian, A., Vega, A., Ubhayakar, N., Xu, P., Liu, A., 2020. Neuroleptic malignant syndrome in a COVID-19 patient. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2020.05.042.
Kaufman-Francis, K., Djordjevic, J.T., Juillard, P., Lev, S., Desmarini, D., 2018. The early innate immune response to, and phagocyte-dependent entry of, cryptococcus neoformans map to the perivascular space of cortical post-capillary venules in neurocryptococcosis. Am. J. Pathol. 188, 1653–1665. https://doi.org/10.1016/j.ajpath.2018.03.015.
Koizumi, S., Shigemoto-Mogami, Y., Nasu-Tada, K., Shinozaki, Y., Ohsawa, K., Tsuda, M., Joshi, B.V., Jacobson, K.A., Kohsaka, S., Inoue, K., 2007. UDP acting at P2Y6 receptors is a mediator of microglial phagocytosis. Nature 446, 1091–1095. https://doi.org/10.1038/nature05704.
Kuboyama, K., Harada, H., Tozaki-Saitoh, H., Tsuda, M., Ushijima, K., Inoue, K., 2011. Astrocytic P2Y1 receptor is involved in the regulation of cytokine/chemokine transcription and cerebral damage in a rat model of cerebral ischemia. J. Cereb. Blood Flow Metab. 31, 1930–1941. https://doi.org/10.1038/jcbfm.2011.49.
Lanser, A.J., Rezende, R.M., Rubino, S., Lorello, P.J., Donnelly, D.J., Xu, H., Lau, L.A., Dulla, C.G., Caldarone, B.J., Robson, S.C., Weiner, H.L., 2017. Disruption of the ATP/adenosine balance in CD39−/− mice is associated with handling-induced seizures. Immunology 152, 589–601. https://doi.org/10.1111/imm.12798.
Li, H., Saucedo-Cuevas, L., Shresta, S., Gleeson, J.G., 2016. The neurobiology of zika virus. Neuron 92, 949–958. https://doi.org/10.1016/j.neuron.2016.11.031.
Liebner, S., Dijkhuizen, R.M., Reiss, Y., Plate, K.H., Agalliu, D., Constantin, G., 2018. Functional morphology of the blood–brain barrier in health and disease. Acta Neuropathol. 135, 311–336. https://doi.org/10.1007/s00401-018-1815-1.
Liu, Y., Chen, G.Q., Liu, B.Y., Chen, Q., Qian, Y.M., Qin, S.S., Liu, C.L., Xu, C.S., 2017. P2X7 receptor in the hippocampus is involved in gp120-induced cognitive dysfunction. Genet. Mol. Res. 16, 1–13. https://doi.org/10.4238/gmr16019356.
Louveau, A., Smirnov, I., Keyes, T.J., Eccles, J.D., Rouhani, S.J., Peske, J.D., Derecki, N.C., Castle, D., Mandell, J.W., Lee, K.S., Harris, T.H., Kipnis, J., 2015. Structural and functional features of central nervous system lymphatic vessels. Nature 523, 337–341. https://doi.org/10.1038/nature14432.
Lucae, S., Salyakina, D., Barden, N., Harvey, M., Gagné, B., Labbé, M., Binder, E.B., Uhr, M., Paez-Pereda, M., Sillaber, I., Ising, M., Brückl, T., Lieb, R., Holsboer, F., Müller-Myhsok, B., 2006. P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. Hum. Mol. Genet. 15, 2438–2445. https://doi.org/10.1093/hmg/ddl166.
Lucas, M.J., Brouwer, M.C., van de Beek, D., 2016. Neurological sequelae of bacterial meningitis. J. Infect. 73, 18–27. https://doi.org/10.1016/j.jinf.2016.04.009.
Luzolo, A.L., Ngoyi, D.M., 2019. Cerebral malaria. Brain Res. Bull. 145, 53–58. https://doi.org/10.1016/j.brainresbull.2019.01.010.
Mackenzie, J.S., 2005. Emerging zoonotic encephalitis viruses: Lessons from Southeast

Asia and Oceania. J. Neurovirol. 11, 434–440. https://doi.org/10.1080/13550280591002487.
Mahamed, D.A., Mills, J.H., Egan, C.E., Denkers, E.Y., Bynoe, M.S., 2012. CD73-generated adenosine facilitates Toxoplasma gondii differentiation to long-lived tissue cysts in the central nervous system. https://doi.org/10.1073/pnas.1205589109/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1205589109.
Mao, L., Wang, M., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Hu, Y., Li, Y., Jin, H., Hu, B., 2020. Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a retrospective case series Study. SSRN Electron. J. https://doi.org/10.2139/ssrn.3544840.
Marín-García, P., Sánchez-Nogueiro, J., Diez, A., León-Otegui, M., Linares, M., García-Palencia, P., Bautista, J.M., Miras-Portugal, M.T., 2009. Altered nucleotide receptor expression in a murine model of cerebral malaria. J. Infect. Dis. 200, 1279–1288. https://doi.org/10.1086/605896.
McCusker, R.H., Kelley, K.W., 2013. Immune-neural connections: How the immune system's response to infectious agents influences behavior. J. Exp. Biol. 216, 84–98. https://doi.org/10.1242/jeb.073411.
Mecha, M., Feliú, A., Iñigo, P.M., Mestre, L., Carrillo-Salinas, F.J., Guaza, C., 2013. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. Neurobiol. Dis. 59, 141–150. https://doi.org/10.1016/j.nbd.2013.06.016.
Meng, F., Guo, Z., Hu, Y., Mai, W., Zhang, Z., Zhang, B., Ge, Q., Lou, H., Guo, F., Chen, J., Duan, S., Gao, Z., 2019. CD73-derived adenosine controls inflammation and neurodegeneration by modulating dopamine signalling. Brain 142, 700–718. https://doi.org/10.1093/brain/awy351.
Monção-Ribeiro, L.C., Cagido, V.R., Lima-Murad, G., Santana, P.T., Riva, D.R., Borojevic, R., Zin, W.A., Cavalcante, M.C.M., Riça, I., Brando-Lima, A.C., Takiya, C.M., Faffe, D.S., Coutinho-Silva, R., 2011. Lipopolysaccharide-induced lung injury: Role of P2X7 receptor. Respir. Physiol. Neurobiol. 179, 314–325. https://doi.org/10.1016/j.resp.2011.09.015.
Moreira-souza, A.C.A., Rangel, P., Rodrigues, S., Figliuolo, V.R., Eduardo, L., Savio, B., Schmitz, F., Takiya, M., Wyse, A.T.S., Vommaro, C., 2019. SHORT communication disruption of purinergic receptor P2X7 signaling increases susceptibility to cerebral toxoplasmosis. Am. J. Pathol. 189, 730–738. https://doi.org/10.1016/j.ajpath.2019.01.001.
Nath, A., 2015. Neuroinfectious diseases: a crisis in neurology and a call for action. JAMA Neurol. 72, 143–144. https://doi.org/10.1001/jamaneurol.2014.3442.
Nath, A., Berger, J., 2004. HIV dementia. Curr. Treat. Options Neurol. 6, 139–151. https://doi.org/10.1007/s11940-004-0023-6.
Nedeljkovic, N., Bjelobaba, I., Subasic, S., Lavrnja, I., Pekovic, S., Stojkov, D., Vjestica, A., Rakic, L., Stojiljkovic, M., 2006. Up-regulation of ectonucleotidase activity after cortical stab injury in rats. Cell Biol. Int. 30, 541–546. https://doi.org/10.1016/j.cellbi.2006.03.001.
Neher, J.J., Neniskyte, U., Hornik, T., Brown, G.C., 2014. Inhibition of UDP/P2Y6 purinergic signaling prevents phagocytosis of viable neurons by activated microglia in vitro and in vivo. Glia 62, 1463–1475. https://doi.org/10.1002/glia.22693.
Nwafor, D.C., Brichacek, A.L., Mohammad, A.S., Griffith, J., Lucke-Wold, B.P., Benkovic, S.A., Geldenhuys, W.J., Lockman, P.R., Brown, C.M., 2019. Targeting the blood-brain barrier to prevent sepsis-associated cognitive impairment. J. Cent. Nerv. Syst. Dis. 11, 1–14. https://doi.org/10.1177/1179573519840652.
Oleszak, E.L., Chang, J.R., Friedman, H., Katsetos, C.D., Platsoucas, C.D., 2004. Theiler's virus infection: a model for multiple sclerosis. Clin. Microbiol. Rev. 17, 174–207. https://doi.org/10.1128/CMR.17.1.174.
Oliveira, C.B., Spanevello, R., Da, A.S., Souza, V.C.G., Pimentel, V.C., Thomé, G.R., Rosa, M., Lopes, S.T.A., Leal, D.B.R., Monteiro, S.G., 2011. Experimental Parasitology Trypanosoma evansi: activities of adenine nucleotide degradation enzymes in cerebral cortex of infected rats. Exp. Parasitol. 128, 225–229. https://doi.org/10.1016/j.exppara.2011.03.007.
Olloquequi, J., Cornejo-Córdova, E., Verdaguer, E., Soriano, F.X., Binvignat, O., Auladell, C., Camins, A., 2018. Excitotoxicity in the pathogenesis of neurological and psychiatric disorders: therapeutic implications. J. Psychopharmacol. 32, 265–275. https://doi.org/10.1177/0269881118754680.
Parvathenani, L.K., Tertyshnikova, S., Greco, C.R., Roberts, S.B., Robertson, B., Posmantur, R., 2003. P2X7 mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease. J. Biol. Chem. 278, 13309–13317. https://doi.org/10.1074/jbc.M209478200.
Pingle, S.C., Jajoo, S., Mukherjea, D., Sniderhan, L.F., Jhaveri, K.A., Marcuzzi, A., Rybak, L.P., Maggirwar, S.B., Ramkumar, V., 2007. Activation of the adenosine A1 receptor inhibits HIV-1 Tat-induced apoptosis by reducing nuclear factor-κB activation and inducible nitric-oxide synthase. Mol. Pharmacol. 72, 856–867. https://doi.org/10.1124/mol.106.031427.
Prinz, M., Priller, J., 2017. The role of peripheral immune cells in the CNS in steady state and disease. Nat. Neurosci. 20, 136–144. https://doi.org/10.1038/nn.4475.
Pu, H., Tian, J., Flora, G., Lee, Y.W., Nath, A., Hennig, B., Toborek, M., 2003. HIV-1 tat protein upregulates inflammatory mediators and induces monocyte invasion into the brain. Mol. Cell. Neurosci. 24, 224–237. https://doi.org/10.1016/S1044-7431(03)00171-4.
Rajasingham, R., Smith, R.M., Park, B.J., Jarvis, J.N., Govender, N.P., Chiller, T.M., Denning, D.W., Loyse, A., Boulware, D.R., 2017. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect. Dis. 17, 873–881. https://doi.org/10.1016/S1473-3099(17)30243-8.
Ralevic, V., Burnstock, G., 1998. Receptors for purines and pyrimidines. Pharmacol. Rev. 50, 413–492.
Rappaport, J., Joseph, J., Croul, S., Alexander, G., Del Valle, L., Amini, S., Khalili, K., 1999. Molecular pathway involved in HIV-1-induced CNS pathology: role of viral regulatory protein. Tat. J. Leukoc. Biol. 65, 458–465. https://doi.org/10.1002/jlb.65.4.458.
Robson, S.C., Sévigny, J., Zimmermann, H., 2006. The E-NTPDase family of ectonucleotidases: structure function relationships and pathophysiological significance. Purinergic Signal. 2, 409–430. https://doi.org/10.1007/s11302-006-9003-5.
Saha, R.N., Pahan, K., 2003. Tumor necrosis factor-α at the crossroads of neuronal life and.pdf. J. Neurochem. 86, 1057–1071.
Salles, É.M. de, Menezes, M.N. de, Siqueira, R., Silva, H.B. da, Amaral, E.P., Castillo-Méndez, S.I., Cunha, I., Cassado, A. dos A., Vieira, F.S., Olivieri, D.N., Tadokoro, C.E., Alvarez, J.M., Coutinho-Silva, R., D'Império-Lima, M.R., 2017. P2X7 receptor drives Th1 cell differentiation and controls the follicular helper T cell population to protect against Plasmodium chabaudi malaria. PLoS Pathog. 13, 1–29. https://doi.org/10.1371/journal.ppat.1006595.
Savio, L.E.B., Andrade, M.G.J., de Andrade Mello, P., Santana, P.T., Moreira-Souza, A.C.A., Kolling, J., Longoni, A., Feldbrügge, L., Wu, Y., Wyse, A.T.S., Robson, S.C., Coutinho-Silva, R., 2017. P2X7 receptor signaling contributes to sepsis-associated brain dysfunction. Mol. Neurobiol. 54, 6459–6470. https://doi.org/10.1007/s12035-016-0168-9.
Savio, L.E.B., Coutinho-Silva, R., 2019. Immunomodulatory effects of P2X7 receptor in intracellular parasite infections. Curr. Opin. Pharmacol. 47, 53–58. https://doi.org/10.1016/j.coph.2019.02.005.
Savio, L.E.B., Mello, P. de A., da Silva, C.G., Coutinho-Silva, R., 2018. The P2X7 receptor in inflammatory diseases: angel or demon? Front. Pharmacol. 9. https://doi.org/10.3389/fphar.2018.00052.
Schlüter, D., Barragan, A., 2019. Advances and challenges in understanding cerebral toxoplasmosis 10, 1–13. https://doi.org/10.3389/fimmu.2019.00242.
Sellner, J., Täuber, M.G., Leib, S.L., 2010. Pathogenesis and pathophysiology of bacterial CNS infections. Handb. Clin. Neurol. 96, 1–16. https://doi.org/10.1016/S0072-9752(09)96001-8.
Sharp, A.J., Polak, P.E., Simonini, V., Lin, S.X., Richardson, J.C., Bongarzone, E.R., Feinstein, D.L., 2008. P2X7 deficiency suppresses development of experimental autoimmune encephalomyelitis. J. Neuroinflamm. 5, 1–13. https://doi.org/10.1186/1742-2094-5-33.
Sheth, S., Brito, R., Mukherjea, D., Rybak, L.P., Ramkumar, V., 2014. Adenosine receptors: expression, function and regulation. Int. J. Mol. Sci. 15, 2024–2052. https://doi.org/10.3390/ijms15022024.
Shi, B., De Girolami, U., He, J., Wang, S., Lorenzo, A., Busciglio, J., Gabuzda, D., 1996. Apoptosis induced by HIV-1 infection of the central nervous system. J. Clin. Invest. 98, 1979–1990. https://doi.org/10.1172/JCI119002.
Shi, L., Wu, B., Yi, Z., Zhao, S., Zou, L., Li, L., Yuan, H., Jia, T., Liu, S., Liu, H., Gao, Y., Li, G., Xu, H., Zhang, C., Liang, S., 2018. P2Y12 shRNA treatment relieved HIV gp120-induced neuropathic pain in rats. Neurochem. Int. 112, 259–266. https://doi.org/10.1016/j.neuint.2017.08.006.
Souza, C.F., Baldissera, M.D., Bottari, N.B., Moreira, K.L.S., da Rocha, M.I.U.M., da Veiga, M.L., Santos, R.C.V., Baldisserotto, B., 2017. Purinergic signaling modulates the cerebral inflammatory response in experimentally infected fish with Streptococcus agalactiae: an attempt to improve the immune response. Mol. Cell. Biochem. 443, 131–138. https://doi.org/10.1007/s11010-017-3217-4.
Stockwell, J., Jakova, E., Cayabyab, F.S., 2017. Adenosine A1 and A2A receptors in the brain: Current research and their role in neurodegeneration. Molecules 22, 1–18. https://doi.org/10.3390/molecules22040676.
Tewari, M., Monika, Varghese, R.K., Menon, M., Seth, P., 2014. Astrocytes mediate HIV-1 Tat-induced neuronal damage via ligand-gated ion channel P2X7R. J. Neurochem. 132, 464–476. https://doi.org/10.1111/jnc.12953.
Tonin, A.A., Da, A.S., Casali, E.A., Silveira, S.S., Moritz, C.E.J., Camillo, G., Flores, M.M., Fighera, R., Thomé, G.R., Morsch, V.M., Rosa, M., Schetinger, C., La, M. De, Vogel, F. S.F., Lopes, S.T.A., 2014. Experimental Parasitology Influence of infection by Toxoplasma gondii on purine levels and E-ADA activity in the brain of mice experimentally infected mice. Exp. Parasitol. https://doi.org/10.1016/j.exppara.2014.04.008.
Tsuda, M., Shigemoto-Mogami, Y., Koizumi, S., Mizokoshi, A., Kohsaka, S., Salter, M.W., Inoue, K., 2003. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. Nature 424, 778–783. https://doi.org/10.1038/nature01786.
Tyebji, S., Seizova, S., Garnham, A.L., Hannan, A.J., Tonkin, C.J., 2019. Brain, Behavior, and Immunity Impaired social behaviour and molecular mediators of associated neural circuits during chronic Toxoplasma gondii infection in female mice. Brain Behav. Immun. 80, 88–108. https://doi.org/10.1016/j.bbi.2019.02.028.
Vavougios, G.D., 2020. Potentially irreversible olfactory and gustatory impairments in COVID-19: Indolent vs. fulminant SARS-CoV-2 neuroinfection. Brain. Behav. Immun. 1–2. https://doi.org/10.1016/j.bbi.2020.04.071.
Vermehren, P., Trotman-Lucas, M., Hechler, B., Gachet, C., Evans, R., Gibson, C., Fern, R., 2018. Cooperation between NMDA-type glutamate and P2 receptors for neuroprotection during stroke: combining astrocyte and neuronal protection. Neuroglia 1, 30–47. https://doi.org/10.3390/neuroglia1010005.
Virgilio, F. Di, Tang, Y., Sarti, A.C., Rossato, M., 2020. A rationale for targeting the P2X7 receptor in Coronavirus disease 19. Br. J. Pharmacol. 19. https://doi.org/10.1111/bph.15138.
Waltl, I., Käufer, C., Gerhauser, I., Chhatbar, C., Ghita, L., Kalinke, U., Löscher, W., 2018. Microglia have a protective role in viral encephalitis-induced seizure development and hippocampal damage. Brain. Behav. Immun. 74, 186–204. https://doi.org/10.1016/j.bbi.2018.09.006.
Wang, H., Hong, L.J., Huang, J.Y., Jiang, Q., Tao, R.R., Tan, C., Lu, N.N., Wang, C.K., Ahmed, M.M., Lu, Y.M., Liu, Z.R., Shi, W.X., Lai, E.Y., Wilcox, C.S., Han, F., 2015. P2RX 7 sensitizes Mac-1/ICAM-1-dependent leukocyte-endothelial adhesion and promotes neurovascular injury during septic encephalopathy. Cell Res. 25, 674–690. https://doi.org/10.1038/cr.2015.61.
Wang, W., Li, G., De, W., Luo, Z., Pan, P., Tian, M., Wang, Y., Xiao, F., Li, A., Wu, K., Liu,

X., Rao, L., Liu, F., Liu, Y., Wu, J., 2018. Zika virus infection induces host inflammatory responses by facilitating NLRP3 inflammasome assembly and interleukin-1β secretion. Nat. Commun. 9. https://doi.org/10.1038/s41467-017-02645-3.

Webster, C.M., Hokari, M., McManus, A., Tang, X.N., Ma, H., Kacimi, R., Yenari, M.A., 2013. Microglial P2Y12 deficiency/inhibition protects against brain ischemia. PLoS One 8. https://doi.org/10.1371/journal.pone.0070927.

Wu, Y., Xu, X., Chen, Z., Duan, J., Hashimoto, K., Yang, L., Liu, C., Yang, C., 2020. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain. Behav. Immun. https://doi.org/10.1016/j.bbi.2020.03.031.

Xiang, Y., Wang, X., Yan, C., Gao, Q., Li, S.A., Liu, J., Zhou, K., Guo, X., Lee, W., Zhang, Y., 2013. Adenosine-5'-triphosphate (ATP) protects mice against bacterial infection by activation of the NLRP3 inflammasome. PLoS One 8. https://doi.org/10.1371/journal.pone.0063759.

Yamane, M., Ogawa, Y., Fukui, M., Kamoi, M., Saijo-Ban, Y., Yaguchi, S., Mukai, S., Kawakita, T., Simmura, S., Tsubota, K., 2015. Long-term rebamipide and diquafosol in two cases of immune-mediated dry eye. Optom. Vis. Sci. 92, S25–S32. https://doi.org/10.1097/OPX.0000000000000523.

Yuan, S.B., Shi, Y., Chen, J., Zhou, X., Li, G., Gelman, B.B., Lisinicchia, J.G., Carlton, S.M., Ferguson, M.R., Tan, A., Sarna, S.K., Tang, S.J., 2014. Gp120 in the pathogenesis of human immunodeficiency virus-associated pain. Ann. Neurol. 75, 837–850. https://doi.org/10.1002/ana.24139.

Zarrinmayeh, H., Territo, P.R., 2020. Purinergic receptors of the central nervous system: biology, PET ligands, and their applications. Mol. Imaging 19, 1–26. https://doi.org/10.1177/1536012120927609.

Zhang, Z., Lei, Y., Yan, C., Mei, X., Jiang, T., Ma, Z., Wang, Q., 2019. Probenecid relieves cerebral dysfunction of sepsis by inhibiting pannexin 1-dependent ATP release. Inflammation 42, 1082–1092. https://doi.org/10.1007/s10753-019-00969-4.

Zhou, F., Liu, X., Gao, L., Zhou, X., Cao, Q., Niu, L., Wang, J., Zuo, D., Li, X., Yang, Y., Hu, M., Yu, Y., Tang, R., Lee, B.H., Choi, B.W., Wang, Y., Izumiya, Y., Xue, M., Zheng, K., Gao, D., 2019. HIV-1 Tat enhances purinergic P2Y4 receptor signaling to mediate inflammatory cytokine production and neuronal damage via PI3K/Akt and ERK MAPK pathways. J. Neuroinflamm. 16, 1–13. https://doi.org/10.1186/s12974-019-1466-8.

Zierhut, M., Dyckhoff, S., Masouris, I., Klein, M., Hammerschmidt, S., Pfister, H.W., Ayata, K., Idzko, M., Koedel, U., 2017. Role of purinergic signaling in experimental pneumococcal meningitis. Sci. Rep. 7, 1–10. https://doi.org/10.1038/srep44625.