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REVIEW

Implications of COVID-19 in Parkinson's disease: the purinergic system in a therapeutic-target perspective to diminish neurodegeneration

Júlia Leão Batista Simões[1] · Geórgia de Carvalho Braga[1] · Samantha Webler Eichler[1] · Gilnei Bruno da Silva[2] · Margarete Dulce Bagatini[3]

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Abstract

The pathophysiology of Parkinson's disease (PD) is marked by degeneration of dopaminergic neurons in the substantia nigra. With advent of COVID-19, which is closely associated with generalized inflammation and multiple organ dysfunctions, the PD patients may develop severe conditions of disease leading to exacerbated degeneration. This condition is caused by the excessive release of pro-inflammatory markers, called cytokine storm, that is capable of triggering neurodegenerative conditions by affecting the blood–brain barrier (BBB). A possible SARS-CoV-2 infection, in serious cases, may compromise the immune system by triggering a hyperstimulation of the neuroimmune response, similar to the pathological processes found in PD. From this perspective, the inflammatory scenario triggers oxidative stress and, consequently, cellular dysfunction in the nervous tissue. The P2X7R seems to be the key mediator of the neuroinflammatory process, as it acts by increasing the concentration of ATP, allowing the influx of Ca^{2+} and the occurrence of mutations in the α-synuclein protein, causing activation of this receptor. Thus, modulation of the purinergic system may have therapeutic potential on the effects of PD, as well as on the damage caused by inflammation of the BBB, which may be able to mitigate the neurodegeneration caused by diseases. Considering all the processes of neuroinflammation, oxidative stress, and mitochondrial dysfunction that PD propose, we can conclude that the P2X7 antagonist acts in the prevention of viral diseases, and it also controls purinergic receptors formed by multi-target compounds directed to self-amplification circuits and, therefore, may be a viable strategy to obtain the desired disease-modifying effect. Thus, purinergic system receptor modulations have a high therapeutic potential for neurodegenerative diseases such as PD.

Highlights

- Parkinson's disease (PD) is a neurodegeneration of public health importance.
- The pathophysiology of PD is associated with oxidative stress and mitochondrial dysfunction.
- COVID-19 increase lethality by the exacerbation of neurodegeneration.
- Purinergic signaling participates of immune response, neuroinflammation, and oxidative stress processes.
- Inhibition of P2X7R reduces exacerbated inflammation and oxidative stress triggered by microglia activity.
- P2Y6R is highly expressed in individuals with PD and may serve as a biomarker for the disease.
- Receptors such as P2Y6, P2X4, and P2Y12 are closely associated with neuroinflammation and neuronal dysfunctions.
- Impaired P2X1 activity enables the accumulation of α-synuclein in neurons.

Keywords Parkinson · Neurodegeneration · COVID-19 · Purinergic system · Free radicals

Abbreviations

A1	Adenosine 1 receptor
A2	Adenosine 2 receptor
A2A	Adenosine 2A receptor
A2B	Adenosine 2B receptor
A3	Adenosine 3 receptor
ACE2	Angiotensin II-converting enzyme
ADA	Adenosine deaminase
Ado	Adenosine nucleoside
ADP	Adenosine diphosphate
α-syn	Alpha-synuclein protein
AMP	Adenosine monophosphate

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ARDS	Acute respiratory distress syndrome
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
cAMP	Cyclic adenosine monophosphate
CD36	Cluster of differentiation 36
CNS	Central nervous system
COVID-19	Coronavirus disease
COX 2	Cyclooxygenase-2
CSF	Cerebrospinal fluid
IFN-I	Type I interferon
IFN-γ	Interferon gamma
IL	Interleukin
IL-1β	Interleukin 1 beta
MERS-CoV	Middle East respiratory syndrome
MHC-I	Major histocompatibility complex class I
MHC-II	Major histocompatibility complex class II
MtDNA	Mitochondrial DNA
NFkB	Kappa-beta nuclear transcription factor
NK	Natural killer
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3
PD	Parkinson's disease
P1	Type 1 purinergic receptor
P2	Type 2 purinergic receptor
ROS	Reactive oxygen species
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2 virus
TLRs	Toll-like receptors
TLR2	Toll-like receptor 2
TLR4	Toll-like receptor 4
TRPA1	Transient receptor potential A1
TNF-α	Tumor necrosis factor alpha

Introduction

Parkinson's disease (PD) is a neurodegeneration of dopaminergic neurons. This disease has a vast symptomatology, with effects on motor and non-motor coordination and appears most often in elderly individuals [1, 2]. In the last three decades, the prevalence of the disease has been growing more and more; however, its pathophysiology is still not completely known, a reality demonstrated in the absence of specific tests for its diagnosis and absence of treatments that reverse the degeneration or attack its underlying cause [2]. Despite this, it is known that PD can originate from the oxidative stress process triggered by the excess of reactive oxygen species (ROS), and that this imbalance can have different causes [3].

Since the COVID-19 pandemic, a greater vulnerability of the elderly and individuals with comorbidities has been noticed, which includes the largest fraction of people with PD. Even if the prevalence of SARS-CoV-2 is not higher in individuals affected by PD, those who were contaminated showed extensive worsening of their neurodegenerative conditions [4]. Therefore, the modulation of pathways shared by the Coronavirus and PD is sought, in order to avoid the worsening of neurodegeneration carriers once they are infected by COVID-19. In this sense, multiple studies demonstrate that oxidative stress and damage to the central nervous system (CNS), characteristics present in PD, can also be triggered by aggressions and inflammatory processes caused by SARS-CoV-2 [5].

In order to search for methods to control this damage, one can consider the influence of the purinergic system on the CNS. In this system, ATP serves as a signaling molecule, which when present in the extracellular environment can activate different receptors, such as P2X7 (P2X7R) [6]. This receptor has a close relationship with inflammatory and immunological processes, being widely activated by COVID-19 in multiple cases, especially in those where the cytokine storm occurs. In addition, studies have already linked its hyperactivation to the presence of neurodegenerative diseases, a niche of which PD is a part [1, 7]. Therefore, our hypothesis is that part of the damage caused to the CNS by COVID-19 is developed through purinergic signaling and that the modulation of this signaling is capable of reducing inflammation and aggression to dopaminergic neurons, preventing the worsening of conditions in patients with PD and the development of this type of degeneration in those infected individuals.

Neuroinflammatory hallmarks and the role of mitochondria in Parkinson's disease

Initially, PD is the second most prevalent progressive neurodegenerative disease globally, surpassed only by Alzheimer's disease, without yet having a treatment that reverses the underlying cause of the disease [8]. In addition, the disease still does not have a specific diagnostic test, being diagnosed based on a combination of clinical findings, nonspecific tests, genetic background, and the presence of risk factors [2]. At the same time, with the emergence of COVID-19, there are many cases of infected individuals who have developed severe neurological manifestations from this contamination, including those with PD [9]. In this sense, there is a need for an in-depth study of the pathophysiology of PD and, especially, its relationship and impacts on those infected with COVID-19, since patients who contracted

the virus showed changes in their PD and worsening in the manifestations of the disease [10].

PD starts from the loss and degeneration of dopaminergic neurons in the substantia nigra of the midbrain, with the reduction of dopaminergic neurotransmitters, resulting in major motor impairments and in non-motor impairments [1, 3]. Among the main symptoms of the disease are tremors, unstable postures, cognitive changes, sleep disturbances, and effects on speech [1]. In addition, the disease is also accompanied by the formation of Lewy bodies in the CNS, composed from the deposition of alpha-synuclein proteins (α-syn), contributing to the evolution of the pathology, neuron degeneration, and cell death [8]. Despite being a disease related to different factors, the underlying cause of the development of this neurodegeneration is not yet known [1, 3].

Evidence from literature have shown that disturbance in the functioning of mitochondria may be involved in pathophysiology of PD [3]. In this light, the main means of mitochondrial influence on the disease is through oxidative stress. From mitochondrial oxidative phosphorylation, there is a release of electrons that, when interacting with oxygen, form ROS. In the case of healthy mitochondria, ROS also exist and have their equilibrium concentration maintained by superoxide dismutases, catalases, and peroxidases, enzymes responsible for the degradation of ROS [11]

In patients with PD, mitochondria produce excessive ROS in mitochondrial complex I, due to mitochondrial dysfunction, or there is suppression of the degradation functions of these substances. Added to this is the increased permeability of the organelle membranes, in order to exacerbate the exit of electrons from the mitochondria and, therefore, the concentration of ROS in the cell, causing damage to the neurons [3, 8]. In addition, the production of ROS is naturally higher in tissues that have a high energy demand, as is the case of dopaminergic neurons, representing an even greater increase in the production of these substances spontaneously [11].

When it comes to the origin of the abnormality in the concentration of ROS, this type of action can be attributed to the inhibition of complex I by specific toxins, or by genetic mutations, the Fenton reaction, and dysfunctions in the mitochondria [8]. Among the causes of mitochondrial dysfunction is excess nitric oxide in the cell. This substance is a versatile mediator formed by enzymes called nitric oxide synthases, acting directly on homeostasis [12]. In a setting of neuroinflammation, microglia and astrocytes produce large amounts of nitric oxide, resulting in increased toxicity and excessive neuronal death from mitochondrial damage and organelle dysfunction. Mesenchymal stem cell therapy improves inflammation and neuronal damage in models of Alzheimer's disease, Parkinson's disease, and other neuroinflammatory disorders, as these can be used as a unique approach to limit neuronal damage caused by neuroinflammation [13]. Another possible pathway for the exacerbation of ROS concentration in cells is due to the Fenton or Haber–Weiss reaction. In this pathway, the accumulation of iron in the cell allows this component to mediate the transformation of non-harmful intracellular substances into ROS, causing an increase in these substances and causing imbalances. Added to this is iron's ability to stimulate the formation of Lewy bodies, structures that are very characteristic of PD [12].

As a consequence of excessive ROS levels in CNS cells, oxidative stress occurs in the neurons. This process has the main consequences of oxidative damage to DNA and lipid peroxidation, in addition to changes in the signaling functions of ROS [14]. Regarding DNA damage, ROSs are able to promote oxidation of cellular DNA bases, as well as the morphological disruption of nucleic acid chains, promoting severe cell damage. Furthermore, oxidative stress is also responsible for damage to mitochondrial DNA (mtDNA), generating aggressions and organelle misconfigurations capable of further increasing the production of ROS, triggering a cycle of damage. Both the cellular DNA damage process and the mtDNA damage process are capable of initiating cellular apoptosis, or tissue autophagy, causing the death of cells damaged by oxidative stress [15]. And such a process, when located in dopaminergic neurons, generates PD [1, 3].

In a second moment, when analyzing the neurological manifestations of contamination by the SARS-CoV-2 virus, approximately one third of those infected had neurological or psychiatric symptoms up to 6 months after contracting the virus, demonstrating the ability of this microorganism to damage the nervous system [5]. In addition, studies have already shown that the virus is capable of penetrating the blood–brain barrier (BBB), a structure responsible for vascularization and protection of the CNS capable of modulating the entry of molecules into the system, and therefore would be able to reach the PD accommodation site [16]. Thus, PD carriers when harmed by contamination by COVID-19 may have worsening of their symptoms and neurodegeneration progress [10].

Among the axes of relationship studied between PD and SARS-CoV-2, the main intersection between the diseases is the development of oxidative stress and neuroinflammation. Once contaminated by COVID-19, the individual has an immune activation from the release of pro-inflammatory cytokines and stimulation of the nuclear factor kappa-beta transcription (NFkB), responsible for the transcription of caspases, cytokines, chemokines, and other inflammatory mediators, causing a very intense inflammatory process [17, 18]. In this context, the aggression and dysfunction of tissues initially unrelated to the virus, as well as the BBB, which, when damaged, allows the entry of microorganisms, neurotoxic substances, and other unwanted cells, causing

damage to the CNS and contributing to neurodegenerative diseases, as is the case of PD [19].

Neuroinflammation plays a significant role in the development of PD since it is closely related to the cascade of events that lead to the degeneration of dopaminergic neurons [20]. There are several factors capable of triggering neuroinflammation, both environmental and genetic [21]. About 5 to 10% of PD cases have this neuronal inflammation originating from known genetic defects, which represent an important fraction of early-onset occurrences [22]. There are some well-known genes associated with this process, such as SNCA, LRRK2, PRKN, PINK1, DJ-I, and leukocyte antigen (HLA), of which LRRK2, PRKN, PINK1, and HLA play important roles in the immune system [22]. Despite this, there is still no complete understanding of how the inflammation generated, both by genetic defects and or sporadic origin, affects these neurons [22] (Table 1).

At the central of PD pathophysiology, there is the microglia, which is an immune cell present in CNS that have specialized function of macrophage-like [23]. Microglia act on the nervous system playing important role as in homeostasis control, tissue reparation, and defense against pathogens [24, 25], but also are associated with neuroinflammation in neurodegenerative disease such as Alzheimer [25] and PD [26]. Regardless of the origin (genetic or sporadic), the presence of several inflammatory molecules, produced by activated microglia and by T lymphocytes [21] in the substantia nigra of the brain, such as tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6, is described by different researchers in autopsied brain findings of people who were affected by PD [22, 27]. Several studies also report the increase of these inflammatory cytokines in the blood and cerebrospinal fluid (CSF) [27].

Several events can trigger the neuroinflammation seen in PD, one of the main ones being the formation of insoluble aggregates of α-syn, also called "Lewy" aggregates, due to their misfolding in the pre-cell terminal-synaptic [20, 27]. One of the main causes of the formation of these Lewy aggregates is a mutation found in the SNCA gene, which is responsible for providing instructions for the production of α-syn [22]. The formation of these aggregates activates innate immune cells such as microglia [21], which, in turn, induce neuroinflammation by stimulating the production of inflammatory components that trigger neuronal death [22].

Activated microglia, in addition to producing inflammatory substances, can damage neurons by other mechanisms, such as the ingestion of damaged neurons, causing neuronal degeneration, the transformation of astrocytes [22], cells of the immune system present in the CNS [20], into a toxic version capable of damaging neurons, promoting mast cell degranulation, stimulating the expression of MHC-II molecules, phagocytosis of aggregated α-syn, disseminating it to healthy neurons [22]. In line with this, several studies carried out in the brains of patients affected by PD, after their death, indicated the excessive presence of activated microglia in the CNS [20]. In the primary stages of PD, these alterations are more present in the olfactory bulb and brainstem. With clinical evolution, they reach the midbrain and, in some cases, the cerebral cortex. This progress occurs as a result of the property that α-syn has to infiltrate neighboring nerve cells, contaminating them in order to expand its effects by expanding the area of action of the activated microglia [21].

Activation of microglia occurs through different pathways, such as receptor, signal transduction, and inflammasome pathways [22]. With regard to the receptor pathway, it is worth mentioning that α-syn aggregates can specifically bind to microglial cell membrane receptors, toll-like receptor 2 (TLR2), toll-like receptor 4 (TLR4), and cluster of differentiation 36 (CD36), in order to promote Fyn kinase recruitment. This protein, through a phosphorylation cascade, manages to increase the production of the inflammatory cytokine IL-1β. It is found, in patients with PD, especially elevated in the striatum, and can also be detected in serum tests [22, 27]. With regard to the signal transduction pathway, it is worth mentioning that α-syn can increase the JAK/STAT transduction pathway in microglia, in order to increase the content of a

Table 1 Genes and proteins involved in the pathophysiology of Parkinson's disease

Gene	Protein	Consequences of mutations
PPARGC1A	PGC-1α	Accumulation of α-synuclein generating Lewy bodies Affects mitochondrial bioenergetic dynamics
PARK2	Parkin	Affects mitochondrial complex I and IV Degenerates dopaminergic neurons Altered mitochondrial volume and membrane potential Deficit in energy production
PINK1	PINK1	Mitochondrial dysfunction α-Synuclein accumulation Increases mitophagy and oxidative stress-induced apoptosis
PARK7	DJ-1	Elevation of reactive species Lysosomal dysfunction Loss of mitochondrial antioxidant function α-Synuclein accumulation

protein called STAT3, which leads to the expression of inflammatory genes and of MHC-II. MHC-II molecules can induce adaptive immune cascades and damage neurons by activating T cells, which have memory of α-syn epitopes [21, 22].

In immune factor context, a multi-protein complex, known as inflammasomes, participates in cellular homeostasis and is involved in cell death [28]. Among them, the NLRP3 is the most inflammasome known [29]. By the oligomerization, inflammassome activates the proteolytic enzyme caspase 1, which promotes the maturation of pro-inflammatory interleukins IL-1β and IL-18 [30, 31]. The NLRP3 activation commonly occurs by the ROS pathway [32], but evidence has shown that α-syn also can activate the NLRP3 increasing IL-1β production in PD [22, 27].

Activated microglia can cause damage by interacting with astrocytes and mast cells [22]. It is worth addressing, in this sense, the link established between the reduction in the number of astrocytes found in the substantia nigra of the brain in PD and the pathogenesis of the disease [20]. Astrocytes detoxify oxygen in healthy people, through the participation of glutathione peroxidase, performing a marked protection for neurons [20]. Inflammatory molecules such as IL-1β, TNF, and C1q complement, which are secreted when microglia are activated, transform astrocyte phenotype into more toxic phenotypic versions, causing them to lose their neuroprotective effects and induce damage to neurons [22]. Furthermore, by producing inflammatory substances, microglia can activate mast cells, which release vasoactive mediators and matrix-degrading enzymes, such as proteases, which can increase the permeability of the BBB, allowing peripherally activated inflammatory components to enter the CNS [22].

In this regard, it is fundamental that changes occur in PD in brain-periphery interactions [21]. Traditionally, the CNS is considered an immunoprivileged site, as it has the BBB that guarantees its protection. However, in case of chronic inflammation in the CNS, the integrity of the BBB is compromised, for example, by the action of mast cells, which allows peripheral immune cells to migrate to the center, among other substances [22]. Furthermore, the existence of the meningeal lymphatic system also corroborates the migration of these pro-inflammatory molecules in case of chronic inflammation [22]. Furthermore, reactive microglia are able to release ROS, which possibly stimulate angiogenesis [21].

Thus, the mitochondrial dysfunctions and oxidative stress discussed above, which, in turn, can also have a genetic or sporadic origin, are associated with neuroinflammation and exacerbate brain damage. α-syn aggregation has the potential to disrupt proteasomal complex-1 function, alter calcium balance in the mitochondrial matrix, and, after a sequence of biological events, cause mitochondrial dysfunction [22]. Large amounts of ROS, mitochondrial fragments, and pieces of mtDNA are produced after impaired mitochondrial function. These ROSs are an important pro-inflammatory stimulus as they can activate nuclear factor κB (NF-κB) [22, 27]. By interacting with toll-like receptors (TLRs), mtDNA fragments can also cause inflammation [22].

Thus, it is convenient to address some important genetic mutations associated with the development of PD in addition to the alteration in the SNCA gene, one of those responsible for the misfolding of α-syn. Mutations in the LRRK2 gene, for example, are a relevant cause of neuroinflammation, and can be found in autosomal dominant cases of Parkinson's, being related to sporadic Parkinson's [22]. Activity in this gene is also increased in other inflammatory diseases, such as Crohn's disease [27]. This gene is expressed in peripheral blood mononuclear cells and is capable of affecting microglial function in different ways. Studies have indicated that the absence of LRRK2 in microglial cells decreases the response to oxidative stress by reducing TNF-α secretion of IL-1β and IL-6. This suggested that microglial LRRK2 may contribute to the pathogenesis of Parkinson's through alterations in the oxidative stress signal [22, 27].

Furthermore, mutations in PRKN and PINK1, responsible for mitochondrial function, in patients affected by PD stand out. Among the attributions of these genes is the response to mitochondrial stress, as they prevent inflammation by removing damaged mitochondria [27]. The lack of these genes can lead to an inflammatory response mediated by type I IFN [22], which induces the expression of COX 2 (cyclooxygenase-2), producing toxic reactive species [27]. The PINK1 gene, in particular, acts more directly on the affected mitochondria, through a process called mitophagy [27]. The more specific role of PRKN, in turn, is encoding an E3 ubiquitin ligase, which plays a neuroprotective role against α-syn toxicity and oxidative stress [27].

Another fundamental gene to be cited in connection with neuroinflammation is the DJ-I gene, responsible for the synthesis of the DJ-I protein. This protein is found in the intermediate space and in the mitochondrial matrix [22], having significant functions such as signaling control of cell membrane receptors, TLR3/4-mediated endocytosis, and production of inflammatory cytokines such as IL-6 and IL-1β [27]. The interruption of mitochondrial dynamics and cell death can occur as a result of a deletion of this gene [22], generating the familial recessive form of PD [27].

There is a genetic alteration commonly seen in individuals affected by PD, the mutation in the human HL region [21], which is associated with an increased risk of late-onset sporadic PD [22]. Several studies, mainly those with an approach called genome-wide association study (GWAS)—which connects diseases to genetic conditions, correlate the genetic function of the immune system with the development of neurodegenerative diseases [21]. Studies even indicate that even alterations in non-coding HLA regions may be related to the development of PD [22]. The main polymorphisms of the MHC alleles are found in LA-DRA,

HLA-DRB5, HLA-DRB1, and HLA-DQ. These genes are involved in adaptive immune response and antigen presentation. The most known mutations alter the synthesis of MHC II, modifying its function in the cell [22].

Furthermore, it is valid to better understand the action of adaptive immunity in PD. Most studies reported the massive presence of T lymphocytes, both TCD4 and TCD8, but not an expressive presence of B lymphocytes [21]. In this context, studies indicate a very important participation of TCD4 molecules in the neurodegeneration process, when they differentiate into Th1 [22] and Th17 [21] cells. Th1 cells produce pro-inflammatory factors such as IFN-γ, which activates MHC I, increasing the number of TCD8 lymphocytes [21, 27], TNF-α, which induces the progressive loss of dopaminergic neurons [27], and IL-2, which plays a crucial role in encouraging T cell proliferation, in particular, in the expansion of Treg (regulatory T) cells, and in mediating inflammation-induced cell death [22, 27]. Th17 cells, on the other hand, increase the neurodegeneration induced by the accumulation of α-syn [21, 27].

Several studies try to understand the relationship between the human microbiome and the greater or lesser probability of developing PD, although this relationship is not well explained [21]. It is a fact that the intestinal microbiome plays a fundamental role in the maturation and differentiation of microglia [22]. Based on this understanding, it is possible to infer that intestinal dysbiosis, that is, the balance in the composition and function of intestinal bacteria is related, in some way, to neuroinflammation. Indeed, this balance has been increasingly recognized as an important mechanism in the pathogenesis of several disorders, especially PD [22].

Furthermore, one of the main forms of access of COVID-19 to the CNS is through the olfactory pathway; in this sense, microorganisms responsible for Influenza A and Ebola also reach the CNS in this way [33]. The microorganisms, in addition to having a common access route, can also result in the development of PD due to structural damage, such as SARS-CoV-2 [34]. Furthermore, as previously mentioned, the Coronavirus is responsible for the cytokine storm and for a generalized inflammatory cascade in the human body [35]. In addition, certain cytokines may be transported across the BBB [36, 37]. The Influenza virus, as well as SARS-Cov-2, can generate generalized inflammation and can activate PD due to this indirect damage [34]. Therefore, it can be assumed that generalized inflammation and the direct effect on the CNS really have the potential to cause the development and worsening of PD, especially through oxidative stress (Fig. 1).

In severe COVID-19 patients, an even greater inflammation can occur, the cytokine storm, characterized by the release of large amounts of cytokines and chemokines in an unregulated way in the body, some of the main ones being interleukin 6 (IL-6), TNF-α, and interferon gamma (IFN-γ) [35]. This imbalance causes an extensive inflammatory process in the individual's body, also capable of promoting nervous tissue aggression and further aggravating problems of this system [5]. Finally, the stress suffered by the body can trigger damage to the pulmonary vascular endothelium, generating hypoxia. Such a picture, added to the previously mentioned aggressions, may be responsible for the loss of balance in neuronal cells and an increase in the production of ROS in the brain, causing damage that, when present on a larger scale and located in dopaminergic neurons, characterizes PD [17].

Therefore, it can be noted that the development of PD has as one of its main origins and precedes the oxidative stress that occurs in dopaminergic neurons, which trigger cell damage and death, resulting in all the symptoms and pathophysiological characteristics of the disease in question. Furthermore, the role of contamination by SARS-Cov-2 as triggering and aggravating this neurodegeneration is clear since it acts as an aggressor of dopaminergic neurons directly and indirectly and promotes the mentioned oxidative stress. Thus, studies are needed regarding treatment methods capable of preventing the development of the mentioned cascade, to avoid the worsening of the patients with the disease, as well as the development of neurological conditions in those who did not have them before, after the contamination by COVID-19.

COVID-19 consequences in Parkinson's disease: what is known so far?

Several works have been bringing to light that COVID-19 may have a neuroinvasive potential capable of acting on neuroinflammation and on BBB dysfunction [38]. The cytokine storm that occurs in severe cases of the disease can reach the CNS through the BBB and culminate in aggravation of PD illness, since they are prone to inflammatory process. Damage to the BBB promotes the entry of pathogenic microbes, the extravasation of red blood cells, and the presence of neurotoxic substances, such as the Fe^{2+} cation, promoting the formation of ROS via Fenton reaction, consequently causing oxidative stress and neurodegeneration [19]. In addition, SARS-CoV-2 infection can add distinct and simultaneous damage, intensify PD motor and non-motor symptoms [39], and increase the predisposition to pneumonia [40]. From this perspective, PD may be a negative factor for poor prognosis by SARS-CoV-2 infection [40].

As discussed in this study, the neurodegenerative processes of PD are directly related to the depletion of neurons in the compact portion of the substantia nigra (substantia nigra pars compact) and other areas of the brain [41]. Both apoptosis and neuronal autophagy are involved in this process. Current theories studying the development of PD neurodegeneration include mitochondrial dysfunction and oxidative stress as possible causes, as there is damage to

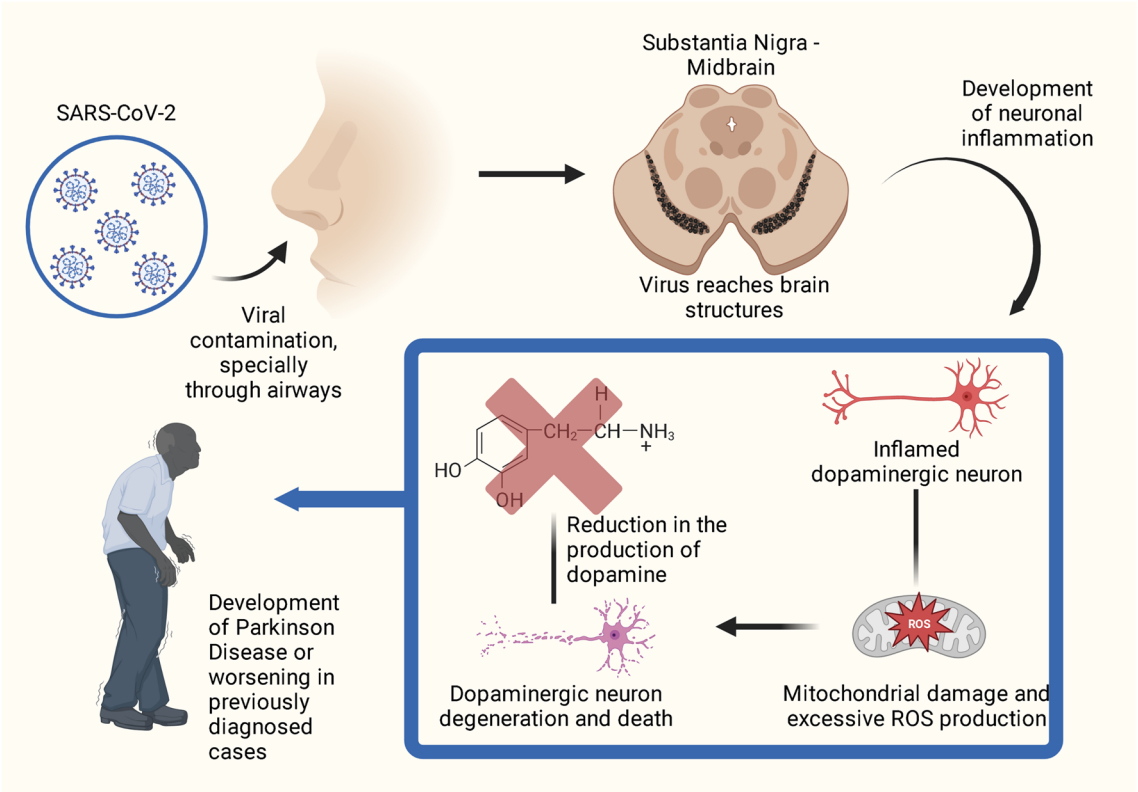

Fig. 1 The hypothetical role of SARS-CoV-2 in mitochondrial damage and in Parkinson's disease. SARS-CoV-2 infects individuals, especially through the airways, being able to reach the brain and trespassing the BBB in an easier way. Once the virus is installed in brain structures, such as the substantia nigra in the midbrain, it is capable of developing inflammatory processes in the dopaminergic neurons in this region. Due to the inflammation of the cells, mitochondria are also affected and damaged, resulting in the excessive formation of ROS. The excess of ROS in the dopaminergic neurons generates a degeneration and death of this tissue. As there is a major loss of dopaminergic neurons, the liberation of dopamine in the midbrain is reduced and compromised, inducing or worsening cases of Parkinson's disease

the BBB in both cases [42]. The BBB is responsible for coordinating the passage of ions, inhibiting the passage of pathogens and ensuring CNS homeostasis [43]. Virus entry into the BBB, as in the case of SARS-CoV-2 infection, is able to deregulate its performance and can lead to several problems, including the influence on neurodegenerative diseases [19], such as PD.

Curiously, previous referred virus entry into the CNS through the BBB can occur in three ways: transcellular migration, paracellular migration, and the Trojan horse strategy, being this last a smart mechanism in which the virus invades the CNS inside a host phagocytic cell [38]. In all entry pathways, cells infected with SARS-CoV-2 secrete interferons I (IFN-1) capable of alerting neighboring cells of contamination, and in a normal immune response process, infected cells are eliminated in order to prevent viral proliferation. However, this immune response triggers the excessive release of both pro-inflammatory markers such as IL-6, TNF-α, and IFN-γ, and anti-inflammatory markers such as IL-2, IL-4, and IL-10. Unlike other similar virus infections, SARS-CoV or MERS-CoV indicate an increase only in pro-inflammatory markers [38]. It is important to highlight that release of cytokines in an immune response is essential for the recognition and subsequent elimination of antigens [44]. However, an exacerbated production of these pro-inflammatory markers, such as occurs in cytokine storms, is capable of promoting inflammation in tissues that have not had contact with the antigen, causing considerable loss of healthy tissue and consequent dysfunction [44] (Fig. 2).

In SARS-CoV-2 infection, we know that the initial response of the defense cells of the affected tissue can be preponderant in defining a case of more severe infection or a more moderate case of the disease (excessive release of IL-6 is extremely harmful) [38, 45]. The release of pro-inflammatory markers involves the functioning of several cells and can cause additional damage if performed in a decompensated way [45]. For example, when the COVID-19 virus binds to its characteristic cellular receptor angiotensin-converting enzyme receptor 2 (ACE2) of lung epithelial cells, it releases IFN-α and IL-1β, which are cytokines capable of

protecting the other parts of the affected tissue through the stimulation of specialized cells such as natural killer (NK) cells; these cells are responsible for even greater release of pro-inflammatory markers, stimulating phagocytic cells, such as macrophages, to release other markers such as IL-6 [45] and cytokine transporter to other tissues, causing systemic dysfunction [44]. This decompensated cytokine transports, in turn, can cause a dysfunction in the BBB, capable of impacting the homeostasis of these vessels, which are so important for the functioning of the CNS [46].

A powerful indicator of inflammation in the CNS is IL-6, which is produced in the CNS by astrocytes and microglia. High levels of IL-6 raise problems such as the passage of antigens to the CNS and the extravasation of red blood cells [38, 43]. Thus, it may be possible that the BBB dysfunction caused by the cytokine storm is mainly due to IL-6. It is important to emphasize that a malfunction of the BBB is capable of releasing neurotoxins in the CNS, which contribute to oxidative stress, a process that drives the characteristic neurodegeneration of PD [19]. Cellular organelles and mainly mitochondria suffer impacts on their functioning due to the effects of the arrival of infection in the cellular environment. Mitochondria participate in the processes of ATP formation and, in addition, are related to the activation of inflammatory processes (inflammasome activation) and apoptosis, being essential for the maintenance of cellular homeostasis [47]. A mitochondrial dysfunction, which may be caused by COVID-19, is capable of intensifying the cytokine storm, as well as promoting cell death, which may also have great impact on PD [48].

Initially, SARS-CoV-2 infection causes changes in calcium homeostasis and provides oxidative stress, as some viral proteins target mitochondria and these organelles are influenced by the cellular physiological environment, which is altered when the cellular machinery is being used by the virus [47]. Viral infections also cause damage to mtDNA, in order to prevent an orderly immune response of the cell, which interferes with the cellular respiration process, as enzymes that participate in the citric acid cycle and the respiratory chain are synthesized from transcription and translation of mtDNA [47]. The action of the virus damages the integrity of mitochondrial membranes, causing dysfunction, which produces ROS, responsible for oxidative stress [49]. Although ROS are important for cellular metabolism in low amounts, a high amount is harmful and can cause damage both to cells infected by SARS-CoV-2 and healthy cells nearby [50]. Thus, there can be cumulative damage that compromises the functionality of organs and systems [47]. This mitochondrial dysfunction ends up disrupting the patient's immune system, causing a storm of cytokines, mechanism responsible for most deaths from COVID-19.

Considering the whole context and urgent necessity of searching for some possible pharmacology treatment, recent studies have hypothesized that the use of vitamin D may be efficient in preventing the chain of events that aggravate COVID-19 cases, from mitochondrial dysfunction to the unregulated production of cytokines, due to its ability to increase the expression of enzyme antioxidants, which can prevent the oxidative stress characteristic of SARS-CoV-2 infection, at least at lung disease levels [47]. However, the systemic proliferation of cytokines in severe cases does not find an effective method of combat in the literature, as the damage caused by the decompensated inflammatory process reaches high levels, even reaching the CNS through the BBB, where there may be irreversible

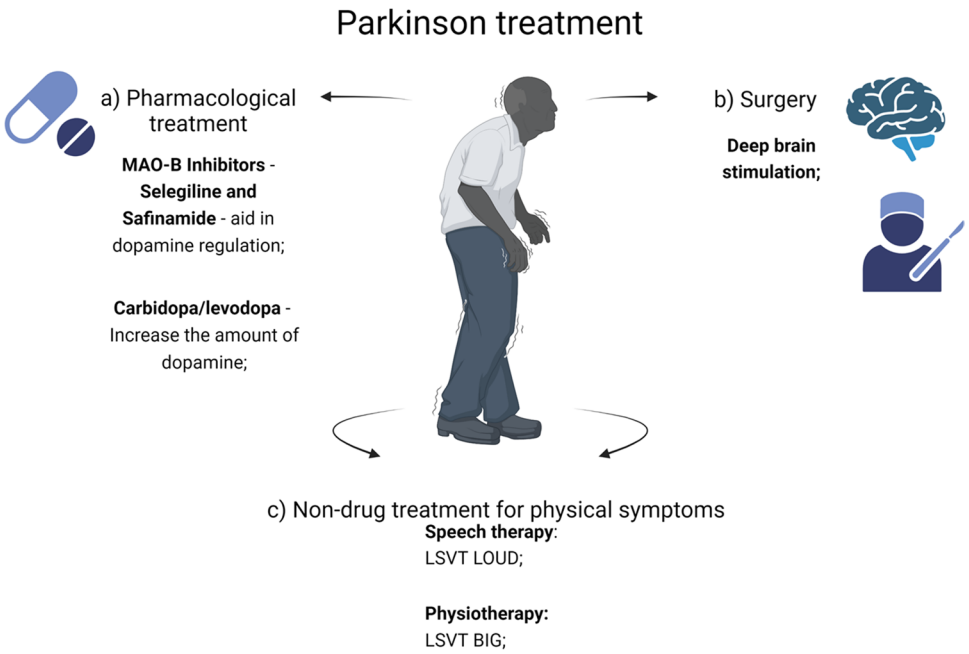

Fig. 2 Current status of Parkinson's disease treatment. This therapeutic process has three main aspects: **a** pharmacological, **b** surgical, and **c** rehabilitation. Regarding drug treatment, MAO-B inhibitors are traditionally used, such as selegiline and safinamide, which are dopamine metabolism regulators. Also, it is very common to use Carbidopa and Levodopa to increase dopamine in the central nervous system. In addition, surgical interventions are used to improve patients' quality of life. Finally, many patients are referred to physical therapy, in the search for improvement of verbal and motor symptoms, such as Lee Silverman Voice Treatment (LSVT)

complications [51]. Infections that cause mitochondrial dysfunction can directly interfere with neurodegenerative diseases such as PD [48]. The impulse of neuronal destruction caused by the fulminant inflammation characteristic of the cytokine storm adds to the apoptosis and autophagy of PD [52], adding simultaneous damages that confer higher mortality and in patients with both PD and COVID-19, than those only with the virus [39]. In addition, motor and non-motor symptoms of patients with PD may be intensified after SARS-CoV-2 infection, as the loss of neurons is increased.

Following these vitamin adjuvant approaches, vitamin C appears to hold promise for treating oxidative stress and COVID-19. It has pleiotropic effects acting, in addition to an antioxidant substance, an anti-inflammatory, and immune support component, as well as a co-factor for mono and dioxygenase enzymes, reducing cellular and organ damage [53]. Previous studies have indicated that vitamin C administration can stabilize oxidative stress in patients with acute respiratory distress syndrome (ARDS) [54]. Furthermore, the production of ROS, which causes oxidative stress, can be extremely harmful. In SARS-CoV-2 infection, the excessive recruitment of defense cells, such as neutrophils, by the cytokine storm is responsible for the formation of ROS, which contribute to the growth of oxidative stress [55]. Still, there is the nuclear translocation of the master redox-sensitive transcription factor (NRF2), responsible for increasing antioxidant protection, as viral infections have inhibitory potential on the action of NRF2, causing a decrease in antioxidant enzymes [56], as well as acting by promoting activating signaling of nuclear factor kappa B (NF-κB), which can increase oxidative and inflammatory processes in infected cell [56]. Recently, Liu et al. [57] performed a prospective randomized placebo-controlled study with COVID-19 patients, in which patients received intravenous vitamin C diluted in sterile water or placebo for 7 days and concluded that this vitamin has the potential to suppress the cytokine storm caused by the disease COVID-19, improving lung function and reducing the risk of ARDS. Considering that oxidative stress plays a possible role in neurodegenerative diseases and the worsening of the oxidative conditions of COVID, vitamin C could be a promising adjunctive therapy.

It is important to clarify that COVID-19 have been showed as a great health challenge on PD illnesses, while robust increased scientific evidences prove that SARS-CoV-2 infection seems to upstream several biochemical pathways that culminate in exacerbation of oxidative stress in patients with this neurodegenerative disease and end in severe cases. Unfortunately, even with efforts, it is necessary to carry out new clinical trials to understand the real beneficial and collateral effects of these supplementations, and PD patients yet are mercy of complications that may cause death. These findings reinforce the importance of seeking to understand the clear mechanism between COVID and oxidative stress exacerbations in PD to improve prognosis in this health context.

Current status of the pharmacological and therapeutic process of Parkinson's disease

The treatment for PD aims to delay or stop the progression of the pathology in those affected, in addition to improving the symptoms, since there is no cure [58]. Conventionally, different areas of health care are integrated to treat the disease and its symptoms, which can be motor and non-motor [58, 59]. Neurologists are responsible for the pharmacological intervention; physical therapists treat motor disorders such as bradykinesia (slowness of movement), hypokinesia (reduced range of motion), and akinesia (involuntary hesitation of movements); and speech therapists treat problems related to vocal softening of the patient—caused, especially, by bradykinesia and hypokinesia in the vocal folds [58, 59].

From this perspective, the disease is associated with several clinical conditions, which can worsen or delay it. Regarding the pathophysiology, PD is directly related to a significant decrease in dopamine receptors in the CNS. In addition, there is evidence that neuroinflammation—caused by the activation of microglia—may contribute to the progression of the disease. Therefore, to better treat the pathology, solutions are used with rehabilitation protocols and with dopamine precursors traditionally. Added to this, it is also common to seek solutions to reduce neuroinflammation from physical exercises and natural medicines [34, 58–62].

Rehabilitation protocols are used by physiotherapists and speech therapists to improve the physical symptoms of the disease. The LSVT LOUD program is used to improve vocal symptoms—applied by a speech therapist under the supervision of a neurologist. This program results in improved voice output and vocal volume [58, 61]. In addition, another similar program is used to improve motor symptoms: LSVT BIG. This protocol is applied by physical therapists under the supervision of neurologists, so that the application of the LSVT BIG results in increased range of motion and its fluidity [58, 61].

Pharmacologically, the motor symptoms of PD are conventionally reduced in dopamine precursors. The drug originally used to treat PD is the injection of apomorphine—a dopamine agonist—with an effect similar to levodopa, but with a shorter duration and mechanism of action different from dopamine agonists [58]. However, the most recurrent procedure is based on the use of the carbidopa line associated with levodopa or a dopamine agonist, since PD is related to a significant decrease in dopamine—a neurotransmitter belonging to the category of catecholamines. The

drug mechanism acts by modulating the enzymatic activity to control dopamine in the CNS [59, 60]. For non-motor symptoms, such as anxiety, apathy, and depression—present in 50% of patients—common in the early stages of Parkinson's disease, non-dopaminergic solutions are used, such as selective serotonin reuptake inhibitors for psychiatric symptoms and cholinesterase inhibitors for cognition, to treat them [58, 60].

In the healthy body, the amino acid tyrosine (Tyr) is transformed, through the enzyme tyrosine hydroxylase, into levodopa (DOPA). From this, the enzyme DOPA decarboxylase removes CO_2 from DOPA, transforming it into dopamine [58]. The combination of drugs carbidopa/levodopa, used in PD, helps to increase the neurotransmitter dopamine in the CNS, with levodopa being a direct precursor to this increase, while carbidopa acts by inhibiting DOPA decarboxylase present in the peripheral nervous system, in order to prevent the peripheral production of dopamine—from levodopa—consequently increasing the amount of dopamine in the CNS. This is because levodopa, instead of being converted to dopamine in the peripheral nervous system, is successfully transported to the CNS where it can finally be converted [58, 59].

In the long term, there may be complications in the use of levodopa, associated with the phenomenon of wasting—the appearance of motor symptoms before the next scheduled dose of levodopa. It is common, in these situations, to change the dosage of levodopa [62]. Furthermore, due to this situation, several dopaminergic and non-dopaminergic pharmacological approaches are employed to treat these complications, such as new formulations of levodopa [59]. Dopamine agonists that bind to dopamine receptors in the CNS are commonly used, but others such as monoamine oxidase (MAO) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and adenosine A2A antagonists are also employed. These are used as monotherapy for various patients. Inhibitors of the enzymes responsible for dopamine inactivation are also used for the treatment of Parkinson's disease. The MAO-B inhibitors Selegiline and Safinamide are used in conjunction with carbidopa/levodopa as they assist in the regulation of dopamine in the peripheral nervous system, increasing the availability of levodopa in the CNS [58, 59].

There is evidence that neuroinflammation contributes to the progression of PD. Although it is not certain whether this neuroinflammation is a consequence of the disease itself or a pathological process resulting from the misfolding of the α-syn, there are studies that indicate that the practice of physical exercises promotes mitigation of this neuroinflammation, since it promotes the inhibition of α-syn accumulation. Aerobic exercises have been shown to be beneficial, in this sense, for neuroprotection [34, 58]. Two immunotherapeutic strategies are currently being explored against α-syn neuroinflammation: active immunization and passive immunization. In active immunization, the patient's own immune system is used to generate antibodies against α-syn. In this case, the AFFITOPE®AFF1 vaccine is applied, which works from the inoculation of α-syn fragments that stimulate the creation of antibodies in the patient. In passive immunization, antibodies are administered directly to the patient [34].

Since neuroinflammation is related to PD, immunomodulatory therapies are promising for improving the condition of the disease [34]. Astrocytes, cells responsible for supporting, nourishing. and sustaining neurons, and microglia, cells responsible for defending the CNS, can cause neuroinflammation and neurodegeneration from the release of compounds such as free radicals [34]. In this context, recent studies demonstrate that dopaminergic receptors are protected from inflammatory responses induced by astrocytes and microglia when exposed to the glucagon-like peptide 1 receptor (GLP1R) agonist NLY0 [34, 58].

Surgical intervention can also be performed in the patient with Parkinson's, especially in the more advanced stages. The procedure employed is deep brain stimulation (DBS) [58]. In this process, an electrode is implanted in the patient's head in order to stimulate electrical impulses. Furthermore, an electrical impulse stimulator is inserted into the subclavian region, and electrodes are inserted into the subcutaneous region [63]. The procedure can be performed unilaterally or bilaterally, being considered reversible, as there is no loss of brain tissue, and the stimulation can be adjusted according to the progression of the disease [58, 63]. DBS typically targets the thalamus, globus pallidus, and subthalamic nucleus [58].

In recent years, pharmacogenetic mechanisms have been increasingly used in the treatment of Parkinson's disease. Since levodopa is encoded by about fourteen genes and may be affected by other pathogenic genes, it is expected that different affected genes can generate different symptoms. Furthermore, each gene is subject to different types of epigenetic mechanisms (DNA methylation, histone and chromatin remodeling, mRNA regulation). In this way, the importance of a specialized treatment for each patient is perceived, in order to improve the effectiveness of this treatment from pharmacogenetics, optimizing the safety of the process [59].

Antiparkinsonian drugs commonly have unwanted side effects and do not promote healing. In this sense, new compounds and alternatives have been studied in order to promote better therapy for patients. Natural medicines with potential efficacy for Parkinson's disease, due to their anti-inflammatory and antioxidant properties, show promise in this context. For example, in vitro studies with the substance Atremorine, which is generated through biotechnological procedures from structural components of

Vicia faba, indicate its ability to prevent and treat PD. The results of these studies demonstrate the ability of Atremorine to protect against dopaminergic neurodegeneration. In addition, Atremorine has also been shown to be a potential treatment for neuropsychic disorders resulting from Parkinson's disease [59]. On the other hand, there is an ongoing study that tries to understand the action of vitamin D3 in the progression of PD. The person with Parkinson's who lacks vitamin D3 has impaired motor function and the severity of the disease increases. People with Parkinson's with higher vitamin D3 have better cognitive development and verbal fluency [64]. Thus, it is interesting to study the complementation of this vitamin during the progression of treatment. Meanwhile, vitamin B1 supplementation is critical for healthy nerves [58].

Two different forms of therapies have been tested in clinical trials: new stem cell therapies and red light helmet therapy. New therapies with stem cells, tested in Japan, using dopaminergic neurons derived from induced pluripotent stem cells, would allow the renewal and replacement of dopaminergic neurons in patients [58]. Therapy using the red light helmet consists of a helmet that emits wavelengths in the infrared and red light range. Preliminary results indicated an improvement in the patient with Parkinson's disease when submitted to this process (Fig. 3) [58].

Thus, it is essential to highlight a new approach to be analyzed for the treatment of PD: purinergic signaling. Purines—an organic compound formed by heterocycles—have neurotransmitter and cotransmitter properties, making their study promising to treat diseases that affect the nervous system [65]. Initially, it is worth noting that adenine and adenosine are important regulators of dopamine transmission in the body. Adenosine has two main receptors: A1 and A2A—related to the transmission of motor impulses in the CNS. The main signaling pathway of this adenosine is the cyclic adenosine monophosphate (cAMP)-dependent pathway [66]. The A2A receptor is associated with PD as it is related to dopaminergic receptors. A2A antagonists have been the subject of research and studies as a complementary treatment for Parkinson's. An inhibition of this receptor interrupted motor impairment in a mouse model of PD generated from the insecticide rotenone. This effect occurs because the inhibition of this receptor is related to the therapeutic increase in levodopa [6, 67].

Therefore, it is notable that many treatments and studies show promise in treating Parkinson's. More clinical trials are needed, mainly involving pharmacogenetics aiming at a more specific treatment, natural substances such as Atremorine [59], stem cell therapies, therapies with specific frequencies of infrared emissions in specific brain regions [58], and receptor inhibitor A2A [6, 66, 67].

Purinergic signaling in Parkinson's disease: from intimate linkage to antioxidant and anti-inflammatory potential therapeutic

The purinergic system is a cell–cell pathway communication involved in cellular responses both health and disease, displaying several biological processes. Most discussed extracellular signaling molecules include nucleotides such as adenosine triphosphate (ATP), adenosine diphosphate (ADP), adenosine monophosphate (AMP), and the nucleoside adenosine (Ado) [6, 68, 69]. The ATP has been considered a key molecule that exhibits influences in immune responses and central tissues, can be released from the inflammatory cells via different mechanisms, such as exocytosis, plasma-membrane channels pannexin, or lysis [6, 69, 70]. Recently, Silva and Manica et al. [71] proved that patients with COVID-19 show alterations in purinergic signaling with increased levels of ATP in serum compared to healthy individuals, which reinforces the role of this signaling cell system in several contexts.

Ubiquitously expressed in most of the body's cells, such as the nervous system [72], the components belonging to this system are divided between receptors, according to the signaling molecule, as well as in enzymes. Thus, the P2 receptor is sensitized by adenine nucleotides, such as ATP, ADP, and AMP, being subdivided into P2X (1–7). In case of the P2Y receptors, they are divided into P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P2Y13, and P2Y14. The P1 group is signaled Ado molecules and differentiated into A1, A2, A2B, and A3 [73]. The levels of signaling molecules are controlled by enzymes known as ectonucleotidases, expressed on the surface of cells. They are nucleoside triphosphate diphosphohydrolase 1 (NTPDase-1/CD39), 5′-nucleotidase (5′-NT/CD73), and adenosine deaminase (ADA) enzymes, which metabolize ATP/ADP into AMP, AMP into Ado, and finally this into inosine, respectively [74–77].

In this context, a well-known receptor is the P2X7R, which is a subtype ionotropic P2X receptor and widely expressed in the human body [78]. The P2X7Rs play many important roles in cells of the central and peripheral nervous system, such as microglia, astrocytes, Schwann cells, and oligodendrocytes [72, 79, 80], and are involved in plenty inflammatory, immune, neurologic, and musculoskeletal disorders [79]. Interestingly, P2X7R activation in an improper situation may trigger the release of ROS and precipitate cytotoxicity mediators [81]. Moreover, adenine transmitters and nerve stimulation in the presence of atropine and guanethidine, nucleotides, and the adenine nucleoside were highlighted as signaling molecules in this system [73]. Thus, ATP and Ado act directly in transmitting information in different processes, such as neuromodulation and neurotransmission. Several physiological and pathological processes

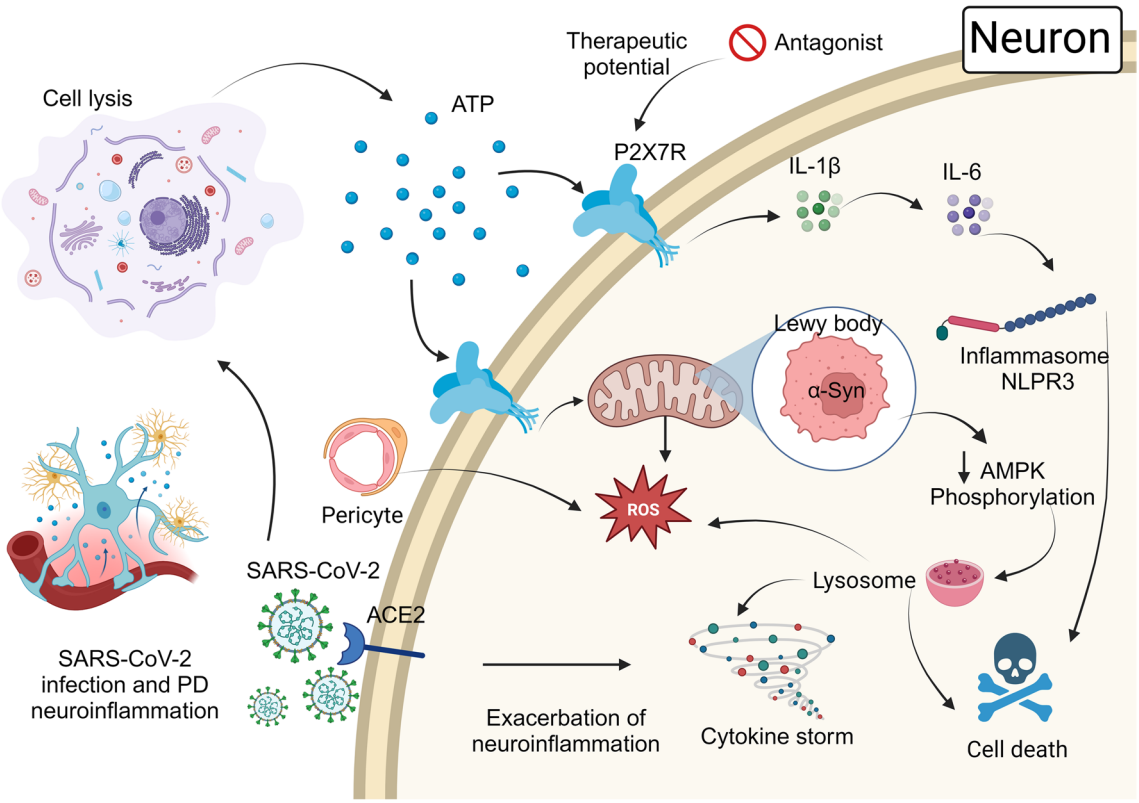

Fig. 3 Role of P2X7 in the progression of PD in its association pathways with the SARS-CoV-2 virus. Neuroinflammation prior to neurodegeneration, potentiated by SARS-CoV-2 infection, causing cell lysis and increased extracellular ATP. This cycle feeds back, and the increase in ATP in the extracellular environment can also accelerate neurons impairment and death, triggering a series of inflammatory cascades through interleukins and mitochondrial and lysosomal dysfunctions. It is observed that mutations in Lewy bodies and α-synuclein (α-syn) protein trigger a decrease in AMPK phosphorylation, which is activated to regulate cellular energy metabolism, generating oxidative stress and an increase in the release of ROS by the mitochondria. Another factor related to the decrease in AMPK phosphorylation is that P2X7R negatively regulates cellular autophagy, triggering processes of apoptosis and ROS increase. Pericytes also influence the formation of ROS, and when the maintenance of phagocytosis is unregulated, this cell participates in the neuroinflammation process. Otherwise, with the entry of ATP, the activation of IL-1β and IL-6 of microglial cells that triggers the activation of the NLRP3 inflammasome that induces pyroptosis (programmed death) and consequently promotes even more release of IL-1β. Both the NLRP3 inflammasome and the dysregulation of the lysosome in the progression of COVID-19, the inflammasome acts as a trigger of the cytokine storm, leaving it very susceptible to the aggravation, whereas in the lysosome, the coronaviruses interact with the cellular autophagy pathway to increase the replication of the virus. The cytokine storm caused by COVID-19 increases the release of extracellular ATP that is regulated by P2X7R. In this way, P2X7R antagonists can be targeted to modulate inflammatory pathways and reduce neurodegenerative effects

can be mediated, especially this receptor, the P2X7R, highlighted for its therapeutic potential in different clinical conditions, such as PD. From this perspective, an ongoing case–control study in which PD patients will be treated with memantine, a dopamine receptor agonist, is currently focusing on understanding the possible influence of this drug on P2X7R-inflammasome activity, as well as on other inflammatory markers [82].

The association of PD with ATP signaling occurs due to the increased concentration of ATP in the extracellular environment, resulting from damage to neuronal tissue or cell lysis due to brain damage or neurodegeneration [83]. Thus, the increase in ATP concentration together with the decrease in the extracellular contractions of Ca^{2+} and Mg^{2+} activates the P2X7R [84]. P2X7R can be expressed in hematopoietic lineage cells and can mediate cell death, regulate inflammatory responses, and even eliminate infected cells [84]. In this sense, by increasing the release of ATP, there is an increase in P2X7R signaling and the triggering of a series of inflammatory cascades through interleukins and mitochondrial and lysosomal dysfunctions, which can be aggravated in a scenario of SARS-CoV-2 infection [85–87].

In addition, the presence of Lewy bodies and α-syn protein in PD pathophysiology is closely associated with P2X7R expression, as this is a target in situations of mitochondrial dysfunction and high levels of oxidative stress [83, 88]. A study demonstrated that pharmacological antagonists of P2X7R and P2Y6R act by preventing cell death in the

SH-SY5Y cell line [85]. Likewise, when triggering a chain response to α-syn neurotoxicity, P2X7R induces the generation of ROS in neurons [83]. Another relevant factor for the increase in extracellular ATP concentration is the induction of increased membrane permeability to hydrophilic solutes, allowing the passage of molecules through macropores. Thus, Ca^{2+} homeostasis is impaired, as well as the individual's immune activity due to the activation of the inflammatory response and the greater free passage of substances through the macropores [89].

In PD and in other diseases that cause neurodegeneration, it is observed that the ATP molecule is released into the extracellular matrix, activating the P2X7R, which triggers the formation of macropores in the plasma membrane. These, in turn, disrupt the ionic balance and trigger cell death (nigrostriatal dopaminergic neuron) [90]. Thus, with the death of this neuron, interleukin 1β (IL-1β) is released, which contributes to an uncontrolled inflammation process and, consequently, a worsening of the degenerative state. In an observed study, the P2X7R antagonist was used as therapy for PD, which works by preventing the depletion of the dopamine store (in animal models of 2,4,5-trihydroxyphenethylamine-6-OHDA) without neutralizing dopaminergic cells loss [90].

Furthermore, to understand the pathology of the disease and how the receptors act, it is necessary to understand the substantia nigra compact (SNc) and the neurons of the substantia nigra reticular (SNr) because it is in this place that dopamine is produced. When there is a loss of dopamine modulation in neurons present in the basal ganglia, the firing of the nervous impulse becomes irregular and explosive, triggering a pathological firing of rigidity and postural instability, characteristic of PD [91]. This issue is also related to microglial activation in the substantia nigra [72]. However, none of these pathways fully explain the firing of the SNr neuron, which is highly dependent on metabolism, but when dopamine modulation is lost, pathological signs include increased burst, irregular firing, and synchronous oscillatory activity in patients and animal models [91].

Otherwise, the formation of Lewy bodies rich in α-syn protein is essential for the performance of P2X7R [83]. This occurs due to an incorrect folding of protofibrils or higher order oligomers that end up causing toxicity to the function of the protein that has a physiological function including the dopamine transporter, also influencing the substantia nigra process and mitochondrial dysfunction, depending on the P2X7R triggering a decreased energy production and cell death [83]. In this matter, modifications such as nitration, phosphorylation, and ubiquitination can occur, which can enhance its pathological accumulation, and at the genetic level, mutations in the gene of this protein can occur, often conferring a familial early PD [92].

The calcium ion participates significantly in the neurodegeneration process and can be modulated by P2X7R [72]. Thus, deregulation of this receptor is present in PD induced by α-syn [88], given the modulation of cell necrosis. From this perspective, there are several targets for Ca^{2+} in cell death signaling, including protein kinases and phosphates, NO synthases, endonucleases, transglutamines, phospholipases, and proteases [93]. P2X7R significantly increases Ca^{2+} influx, whereas the P2X7 antagonist prevents Ca^{2+} influx. Therefore, P2X7R is understood to play a role in Ca^{2+} imbalance [88]. Likewise, with oxygen–glucose deprivation, a post-anoptic influx current is generated, accompanied by a massive influx of Ca^{2+}, resulting in neuronal death, and it is also possible to observe Ca^{2+} signaling in its influx for the formation of inflammasomes [94].

Pro-inflammatory cytokines are also present in PD because an activation of IL-1β of microglial cells occurs in the inflammatory response [85, 95]. This triggers inflammasome activation, mainly NLRP3, which induces pyroptosis (programmed death) and consequently promotes even more release of IL-1β [94]. Initially, the stimulation of the TLR4 leads to the accumulation of pro-IL-1β in the cell cytoplasm; then in the activation of the nucleotide, there is a leucine-binding-rich repeat, NLRP3 inflammasome [72]. The stimulation of this inflammasome initiates the cleavage of pro-caspase-1 to caspase-1 and the subsequent enzymatic degradation of pro-IL-1β to mature IL-1β, by proteolysis induced by caspase-1. In addition, P2X7R influences IL-1b production and release [96, 97].

For inflammasomes to be activated, there must be potassium efflux, increased intracellular calcium and ROS, Ca^{2+} signaling, and mitochondrial dysfunction, among other activators. Potassium efflux reduces its concentration in the cytoplasm and ATP, through P2X7R, allows K^+ efflux to occur [94]. It is possible to observe these pro-inflammatory factors aggravated in the pulmonary invasion of SARS-Cov-2, as well as a hyperactivation of P2X7R [98]. In patients with COVID-19, activation of P2X7R in the NLRP3 inflammasome is a trigger of cytokine storm, leaving it very susceptible to the aggravation of this pathological condition [87].

Furthermore, it is understood the role of microglia in the progression of PD and how purinergic system therapies can act on this mechanism. Microglia are the resident immune cells of the CNS, in PD, they have the role of mediating the inflammatory response [99]. Together with interleukins, inflammasomes, in microglia they increase the secretion of pro-inflammatory cytokines associated with neurodegeneration [100]. We can therefore infer that P2X7 is involved in microglia activation, as the preferential location of P2X7Rs in the CNS is in microglia, the resident macrophages of the brain [85]. Microglial P2X7R acts as a pattern recognition receptor, which is activated by a high concentration

of extracellular ATP released from cells dying due to brain damage or neurodegeneration [89, 101]. Then, in microglial extracellular α-syn, P2X7R stimulation increased oxidative stress, which was prevented with the use of its antagonist [65].

It is known that the protein α-syn is present in mitochondria and extracellularly, and induces changes in the activity of P2X7R. Likewise, dysregulation of this receptor also contributes to neuronal cells [83]. Studies show that this protein decreases mitochondrial activity and consequently ATP synthesis; however, it increases oxidative stress; it is remarkable that P2X7R blockers reverse this mechanism [83]. Another important point to be related to the decrease in ATP synthesis is the activation of AMPK, which is activated to regulate cellular energy metabolism. It was then noticed that α-syn does not change the level of AMPK protein but significantly decreases its phosphorylation [83]. Mitochondrial damage caused by α-syn due to activation of the mitochondrial pathway of apoptosis is the main cause of neurodegeneration [102]. This occurs when α-syn is activated and can be described as a decline in mitochondrial respiration due to depolarization and disturbances in the activity of the mitochondrial complex and an increase in free radical production [103].

Oxidative stress is linked to the processes that occur with the α-syn protein, as there is growing evidence that mitochondrial damage followed by apoptosis is the main cause of α-syn-evoked neurodegeneration [83]. Thus, this protein stimulates P2X7R, which consequently increases oxidative stress [65]. Also, when analyzing a more general aspect, with oxidative stress being closely related to mitochondria and being a target and source of ROS, it is based on the role of oxidative stress in stimulating apoptosis, because together with mitochondria, oxidative stress is the main cause of neurodegeneration caused by α-syn [104]. Thus, by increasing the oxidative stress, there is the stimulation of microglial P2X7R by extracellular α-syn, and as prevention, there is the P2X7R antagonist [65], such as usual anti-Parkinson treatment [105]. Also, the influx of Ca^{2+} is relevant in this process, which will be discussed later, once that it is related to P2X7R in neuronal cells influencing the oxidative stress process, as it induces the production of extracellular ATP [83].

PD is also involved in microglial lysosomal dysfunction; studies indicate *that* CaMKK and mitoROS may contribute independently in P2X7-mediated AMPK activation [81]. P2X7 causes lysosomal alkalinization that negatively regulates autophagy, as it acts in the induction of cellular stress events to impair lysosomal function [81]. Thus, evidence from studies suggests that coronaviruses interact with the cellular autophagy pathway to increase virus replication [106]. It is possible to explain this issue because the development of endoplasmic reticulum-derived double membrane vesicles that serve as a site of replication in the host cytoplasm is so similar to the development of the autophagosome that it suggests that coronaviruses are mimicking the cellular autophagy pathway [106].

The human coronavirus presents neurotropism, and post mortem studies reveal hemorrhagic lesions accompanied by neuronal lesions and inflammation, characteristic of neurodegenerative diseases [107, 108]. The complications of COVID-19 can be associated with neurodegenerative diseases, including Parkinson's. However, there is also a relationship between P2X7 hyperactivation and inflammatory processes, given that when ATP is released, it induces inflammasome activation [89]. The P2X7R and its activation induced by viral infection leads to molecular activation and behavioral changes in the NLRP3 inflammasome present in patients with COVID-19, which can be, mainly from the neuroimmune response, formation of ROS and glutamate release [87, 109]. Thus, excessive glutamate amount exhibits cytotoxic causing cellular damage and releasing of more levels of ROS [110]. This imbalanced condition can contribute to progress of PD.

In addition to the inflammasome, SARS-CoV-2 also interacts with macrophages and microglial cells [111]. In the same way that the process of an infection occurs, there are similar aspects to the neurodegeneration process. The similarity can be found in the increase in ATP levels in both situations [86, 87]. In patients with COVID-19 and PD, NLRP3 inflammasome as a trigger of cytokine storm, which can be induced by activation of P2X7R, peak protein SARS-CoV-2 interacts with ACE2, and microglial cells and macrophages can potentiate the immune response activating the NLRP3 [111]. Activation of P2X7R triggers a signal necessary for the efficient stimulation of the NLRP3 inflammasome resulting in the release of pro-inflammatory cytokines, through an efflux of K^+ [87, 109]. The activation mechanism of the NLRP3 inflammasome occurs through the cleavage of the fragments of the complement component 3a and 5a of these same fragments (C3a and C5a), and the non-lytic membrane attacks complex C5b-C9 by ComC [111].

It is possible to associate NLRP3 inflammasome activation with IL-1 release as it is the effector of IL-1 secretion; they have been associated with immune dysfunction in the pathogenesis of virus-induced acute respiratory distress syndrome and acute lung injury [112]. Another process mediated by P2X7R is the release of microparticles by inflammatory cells, which have IL-1β and, after stimulation by P2X7R, are an important secretory pathway for monocyte cytokines [113]. In studies, there is a hypothesis that the cytokine storm induced by viral infection can stimulate neuroinflammation and neuronal death, leading to the development of diseases such as PD [114, 115]. This neuroinflammation can be induced by the activation of P2X7R, and the antagonist of this receptor can be a therapeutic approach for

treatment [84, 116]. It can also be observed an aggravation in the case of Parkinsonism after infection by the virus or a greater propensity to develop Parkinson after the neurodegeneration is already established [117].

The first important point is based on similarities between the purinergic signaling, PD, and SARS-CoV-2 virus infection, since both have an increase in ATP in the extracellular environment [114]. In the continuation of this process, inducing the formation of inflammasomes and activation of microglia cells, further providing an oxidative stress in the mitochondrial pathways triggering a nigrostriatal degeneration, consequently trigger an imbalance in the balance of ions such as calcium influx and potassium efflux [72, 88, 94]. Notably, the cytokine storm related to SARS-CoV-2 infection increases BBB permeability allowing neuroinvasion of virus-infected peripheral immune cells, thereby resulting in neuroinflammation and neurodegeneration [95].

There is an essential expression of P2X7R in macrophages located in peripheral tissue, such as Kupffer cells of the liver, marginal zone macrophages of the spleen, alveolar macrophages of the lung, and central tissue (microglia) [89]. They may present as M1 (pro-inflammatory; classic) or M2 (anti-inflammatory; alternatively activated) myopic. P2X7 in these cells responds to high concentrations of extracellular ATP under pathological conditions, resulting in non-selective fluxes of cations (Na^+, Ca^{2+}, K^+). Most peripheral inflammatory diseases share the same classical inflammatory pathway in macrophages with the following components: P2X7R stimulation, NLRP3 and caspase-1 activation, and IL-1/IL-18 release [118].

In inflammatory processes with even higher ATP concentrations, the activation of P2X7Rs, especially after repetitive agonist application, leads to the opening of membrane pores permeable to more than 900 Da molecules. In this dynamic, other membrane channels are activated, such as P2X4R, transient receptor potential A1 (TRPA1), pannexin-1 hemichannel, and chloride channel ANO6 [118]. From this perspective, P2X7Rs located in macrophages must be co-activated with the TLR4 to induce the formation of NLRP3, which then activates the lipopolysaccharide-degrading caspase-1 interleukin-1 to lead to the release of IL-1 [118]. Thus, the modulation of P2X7R can act peripherally and centrally since, especially during the cytokine storm, the application of P2X7R blockers can hinder the extent of cytokine release from peripheral macrophages, consequently preventing damage. To the BBB, the access of viral particles and pro-inflammatory mediators to the CNS is restricted, as an indirect effect, limiting neuroinflammation.

Another point of analysis is the function of P2X7 signaling related to BBB dysfunction; the activation of P2X7R promotes the release of IL-1β that induces the secretion of MMM-9 and the interruption of BBB [84]. It is possible to explain this phenomenon due to the triggering of MMM-9 in occluding degradation and consequently protein degradation and BBB dysfunction [95]. Considering the modulation of P2X7R, they regulate the physiological and pathological functions of inflammation by monitoring infiltrating immune cells, which helps in the changes in BBB permeability [85]. Some cells influence this process of maintenance and formation of the BBB; the P2X7R can prevent the degradation of collagen IV among other proteins, important for the stability of pericytes, which are essential cells for the formation and function and maintenance of the BBB [85]. The importance of pericytes is associated with the modulation of phagocytosis, the expression of adhesion molecules, and stimulating the generation of ROS, so it participates in neuroinflammation processes [119].

Finally, as a result of all this mechanism that occurs simultaneously, it culminates in neurodegeneration and neuronal death [83, 104]. Importantly, α-syn proteins, together with Lewy bodies, induce several processes such as oxidative stress, which has a large proportion of ROSs that are toxic to cells because they present in higher levels [83]. Thus, with this cascade effect, they perform this neurodegeneration process in PD (Fig. 3) (Table 2).

Furthermore, besides P2X7R, other purinoreceptors must be considered in the context of PD pathophysiology. In this sense, P2Y6 receptors (P2Y6R) have already been linked to a neuroinflammatory scenario as well [65]. According to studies, P2Y6R is highly expressed in individuals with PD, which may represent that these receptor activities can serve as a biomarker for the disease [120]. In the light of that, these structures were already associated to oxidative stress, proinflammatory cytokine release leading to neuroinflammatory conditions, and cellular death by other researches, dysfunctions capable of damaging DA neurons and the CNS, leading to PD [65, 121]. Moreover, studies evaluating the blockage of this receptor have found significant reduction of neuroinflammation, corroborating the exposed idea [36]. Considering that, P2Y6R activity represents another possible purinergic pathway for neuroinflammation to be developed and, consequently, trigger PD.

Another important P2X receptor in the context of PD and neurodegeneration is P2X4. These receptors are present in many parts of the CNS, and have presented a relationship with neuronal death [122]. Initially, these receptors are apparently activated by neuronal damage conditions [122]. Considering that the deposition of substances on the brain, such as Aβ aggregates as revealed by studies evaluating the effect of these receptors in Alzheimer's disease, triggers the action of P2X4 receptors (P2X4R), it is possible that the accumulation of substances present in PD can also cause harm and stimulate the activity of these receptors [122]. In this context, Varma and colleagues [122] have found that the hyperactivation of this receptor, induced by harmful

conditions, is present in cases of neural death, as neurodegenerative diseases, being linked to the process of cellular death [122]. Hence, it can be concluded that P2X4R is initially responsible for cellular homeostasis, nonetheless, when excessively induced by neurodegenerative conditions, can affect the CNS negatively and exacerbate the development of neurologic conditions.

Moreover, P2Y12 receptors (P2Y12R) are also relevant structures in the scenario of neuroinflammation, presenting a behavior similar to the expressed by P2X4R. These receptors are highly present in microglia and have been linked to neuronal dysfunctions, since they can activate microglia activity in pathological conditions, indicating the presence of damage to brain cells and aiming at controlling the harmful situation [123]. Therefore, the initial intention of P2Y12R is essential for the preservation of the protection of the CNS [124]. However, studies with mice have indicated that the continuous activation of these receptors, along with the maintenance of a long induction of microglia activity, can lead to neuroinflammation [124]. The findings of Iring and colleagues [124] have indicated that the ideal level of P2Y12R activity is fundamental for the correct balance between anti and pro-inflammatory conditions; otherwise, it can lead to an important release of pro-inflammatory cytokines when overstimulated, which culminates in neuroinflammation and neurodegenerative diseases, such as PD [124].

In addition to the mentioned receptors, another possible target to be evaluated is the modulation of P2X1 receptor (P2X1R) activities, less connected to the development of a neuroinflammatory condition, such as the others, but linked to important cellular dysfunctions. These receptors are highly expressed in the striatum and the substantia nigra in the CNS, regions related to the development of PD, when disbalanced [65]. In this regard, studies have shown that higher levels of extracellular ATP are capable of inducing the activation of P2X1R in the brain, which are responsible for modifying lysosomal actions inside the cell [125]. In regular conditions, this organelle would be able to avoid the accumulation of α-synuclein in neurons; however, due to the actions of P2X1R, this function is impaired, leading to the development of one of the main hallmarks of PD installation, the accumulation of this substance capable of triggering neurodegeneration and compromising the activities of DA neurons [65, 125]. Thus, despite the protagonism of P2X7R activities in most inflammatory and harmful neurodegenerative conditions, other receptors can serve as potential pharmacological targets against PD and must not be forgotten.

Future proposals

Based on the data presented, P2X7 is involved in the process of oxidative stress and neuroinflammation. Thus, it is possible to think of a therapeutic potential based on its modulation, given the close association between P2X7R and PD exacerbation. In addition to the SARS-Cov-2 infection progression process, systemic inflammation activates this receptor, which can be approached as a therapy for COVID-19. Takin into considerations, the P2X7R antagonist may have a chance, at least for the compassionate treatment of patients with COVID-19 with rapidly evolving ARDS [126]. The clinical symptoms of PD occur due to the death of neurons in the substantia nigra as the synthesis of pro-inflammatory cytokines depends on purinergic signaling, such as P2X7R [72, 127].

The exacerbated activation of P2X7R can promote microglial proliferation and release of cytokines and ROS that culminate in increased cell death induction, thus offering progression in the neurodegeneration process [95]. Inhibition of P2X7R reversed apomorphine-induced rotation, predicting possible therapeutic applications in animal studies with PD [90]. Furthermore, results reveal that P2X7R of extracellular ATP and inhibition of ATP degradation are important molecular processes involved in deleterious signaling, so anti-purinergic therapy can be an effective treatment for neurodegenerative diseases [88].

Through P2X7, by the pleiotropic action, extracellular ATP has great potential to protect the host from viral infection and act in the prevention of viral diseases [84, 128].

Table 2 Action and consequence of the processes that occur by activating the P2X7R

Elements	Receptor activity	Consequences
Ca^{2+}	Increased	Calcium influx Opening of micropores Output of intracellular ions and metabolites
Lewy bodies	Increased	Increases toxicity Decreases energy production Cell death
α-Synuclein	Increased	Decreases mitochondrial activity Decreases ATP synthesis Decreases AMPK phosphorylation
IL-1β	Increased	Activation of the NLRP3 inflammasome Induces apoptosis More IL-1β release

Furthermore, the control of purinergic receptors formed by multi-target compounds directed to auto-amplification circuits may be a viable strategy to obtain the desired disease-modifying effect [65]. P2X7R is the key mediator of the neuroinflammatory process as a possible consequence of SARS-CoV-2 infection; combined with PD, it is possible to state that the hyperstimulation of the neuroimmune response observed during viral infection and in mental disorders may be mediated by the activation of P2X7R [86, 87].

Conclusion

In severe cases of COVID-19, the excessive and uncoordinated release of pro-inflammatory markers, called cytokine storm, by macrophages is responsible for causing damage to various tissues in the body. Upon reaching the BBB, the pro-inflammatory markers cross the bloodstream and enter the CNS, promoting greater release of these same markers by astrocytes and microglial cells. The cytokine storm in the CNS is responsible for the oxidation and degeneration of neurons. As a result, patients with PD may have their neurodegenerative condition aggravated.

Furthermore, it is clear how oxidative stress and organelle dysfunction, such as mitochondria and lysosomes, interrelate in the pathophysiology of PD. In this case, the damaged mitochondria and lysosomal organelles act as propellants for the increase of reactive species (ROS and RNS), as well as decreasing the endogenous attenuation mechanisms of these compounds. Thus, there is widespread damage to dopaminergic neurons that are related to voluntary movement. In these cells, there will be, therefore, accumulations of α-syn forming Lewy bodies. It is worth noting that the main region affected by these phenomena is the compact part of the substantia nigra of the midbrain. These occurrences will, therefore, play a strong role in the development of PD pathophysiology.

It is noteworthy that P2X7R has great future potential as a therapy against PD in association with COVID-19, due to its process of modulating both molecules in the entry and exit of cells, as well as the expression of proteins that trigger cell death. Thus, with the modulation of this receptor, it is possible that the pathological process of PD, which is aggravated by COVID-19 due to cytokine storm and the systemic neuroinflammatory process, is prevented.

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Author contribution JLBS had the idea for the article. JLBS, GCB, SWE, GBS and MDB performed the literature search and data analysis, drafted and critically revised the work.

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Data availability All data used in this work is mentioned in the reference section and is available online in scientific databases.

Declarations

Ethics approval Not applicable.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

Consent for publication An informed consent and a consent to publish were obtained from each of the participants.

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Júlia Leão Batista Simões academic in the tenth phase of medicine at the Federal University of Fronteira Sul. She has been conducting research since the beginning of graduation, presenting relevant articles that correlate pathologies in the COVID-19 pandemic with possible therapies by modulating the purinergic system. She is currently an AT fellow by CNPq and is working on writing chapters for books and manuscripts that correlate potential adjuvant therapies and diseases that are strongly highlighted in the literature.

Authors and Affiliations

Júlia Leão Batista Simões[1] · Geórgia de Carvalho Braga[1] · Samantha Webler Eichler[1] · Gilnei Bruno da Silva[2] · Margarete Dulce Bagatini[3]

✉ Margarete Dulce Bagatini
margaretebagatini@yahoo.com.br

Júlia Leão Batista Simões
julialeaobatistasimoes@gmail.com

Geórgia de Carvalho Braga
braga.georgia18@gmail.com

Samantha Webler Eichler
sahwebler@gmail.com

Gilnei Bruno da Silva
gilneibrunosilva@hotmail.com

[1] Medical School, Federal University of Fronteira Sul, Chapecó, SC, Brazil

[2] Multicentric Postgraduate Program in Biochemistry and Molecular Biology, State University of Santa Catarina, Lages, SC, Brazil

[3] Graduate Program in Biomedical Sciences, Federal University of Fronteira Sul, Chapecó, SC, Brazil