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The role and therapeutic potential of connexins, pannexins and their channels in Parkinson's disease

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ABSTRACT

Lack of effective medication for slowing down progression of Parkinson's disease (PD) as a highly prevalent neurodegenerative disorder requires novel avenues of scientific investigation to elucidate the underlying molecular and cellular mechanisms. Studying connexins, pannexins and their channels has uncovered their potential role in mediating communication and signaling pathways that drive neurodegenerative diseases, including PD. Indeed, given their critical role in tissue homeostasis, it is not surprising that connexins, pannexins and their channels are frequently involved in pathological processes. For this reason, pharmacological tools to further clarify their functions and to validate connexins, pannexins and their channels as drug targets for the development of novel therapies for PD treatment are urgently needed. In this paper, a state-of-the-art overview is provided of current neuropathological and molecular understanding of PD. Focus is put on the roles of connexins, pannexins and their channels, in particular in the development of potential innovative disease-modifying therapies for PD treatment.

1. Introduction

Parkinson's disease (PD) is one of the most common neurologic condition in individuals over the age of 60 years and affects one million inhabitants of the United States [1]. Compelling evidence shows the association between exposure to pesticides and other environmental chemicals, and PD [2]. Inflammatory responses, oxidative hazard and apoptosis underlie the pathogenesis of PD [3]. Recent studies also revealed that gap junctions and connexin hemichannels are involved in various neurological diseases, including Alzheimer's disease and PD [4–6]. Gap junctions are intercellular membrane channels allowing cells to directly communicate with neighboring cells [7]. Gap junctions consist of 2 hemichannels of adjacent cells, which in turn are built up by 6 connexin proteins. Gap junctional communication plays numerous important roles in preserving physiological functions, including proliferation, migration and differentiation. Interestingly, connexin hemichannels, in addition to their role as structural precursors of gap junctions, also present a pathway for communication, albeit between the cytosol of an individual and its extracellular environment. Unlike gap junctions, connexin hemichannels become particularly active in pathological conditions, including inflammation and cell death [7–10]. In recent years, pannexins have also emerged as goal keepers of tissue homeostasis and disease. Pannexins form hexameric channels linking the intracellular and extracellular space, and are involved in normal differentiation and development [11]. In neurodegenerative disease, pannexin channels display aberrant functioning and may be etiologic in PD. The purpose of this review paper is to highlight possible functions of connexins, pannexins and their channels in PD etiology, and to outline important gaps in our understanding of their roles in the development of neurons, which has important implications for the establishment of new treatment approaches for neurodegenerative diseases.

2. Parkinson's disease

PD is a dilapidating neurodegenerative disorder featured by the progressive loss of dopaminergic neurons in the striatum and substantia nigra [12]. The typical formation of cytoplasmic protein-based

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inclusions, known as α-synuclein (Lewy bodies), is another hallmark of the disease. PD is the most prevalent neurodegenerative disease worldwide after Alzheimer's disease [13]. Several motor (postural and movement disability) and non-motor (depression, psychosis and dementia) symptoms underlie the clinical manifestation of PD [13]. Reactive astrocytes in the substantia nigra are the main actors involved in the pathogenesis of PD [14]. However, their role in neural survival remains obscure. Clues coming from studies using mouse models of PD have revealed both beneficial and detrimental effects of astrocytes in this context [15]. Induction of oxidative stress, cytokine liberation and apoptosis in dopaminergic neurons have been listed as unfavorable effects of astrocytes, whereas reuptake of glutamate, promotion of antioxidant enzymes, heat shock proteins, and growth factor production have been suggested as beneficial in PD [16–18].

Although the exact mechanism of PD at the molecular level has not yet been elucidated comprehensively, inflammation, oxidative stress and accumulation of α-synuclein are considered as key events in its pathogenesis [19]. *Postmortem* studies of PD patients have shown substantial proliferation of microglia and reactive amoeboid macrophages in the substantia nigra [20]. These activated glial cells can elicit production of inflammatory cytokines [21]. Enhanced mobilization and circulation of inflammatory cytokines as well as local inflammation are cornerstones of the inflammatory response. The connection between neurodegenerative disease and circulating inflammatory cytokines complies with disturbances in the integrity of the vascular bed [22], since instability of blood vessels and leakiness in the blood-brain barrier (BBB) permits the entrance of peripheral inflammatory proteins and cytotoxic cells to the brain. Moreover, the release of inflammatory cytokines from activated glial cells disrupts brain capillaries, which in turn increases the infiltration of circulating cells [23]. Pathological alterations in the cerebral cortex capillaries have been reported to occur in PD and other neurodegenerative diseases [24–26]. These changes might influence the transportation of toxic compounds as well as nutrients in PD [27]. In a 6-hydroxydopamine model of PD, disruption of the BBB has been shown to enhance disease progression [28].

Modulation of inflammatory responses has been identified as an important target to tackle neurodegenerative disease. It has been demonstrated that the amount of tumor necrosis factor-α (TNF-α) is considerably higher in the striatum and cerebrospinal fluid (CSF) of PD patients in comparison with healthy individuals [29]. Also, levels of interleukin 1β (IL-1β) and IL-6 have been reported to increase significantly in the caudate nucleus of PD patients. The microglial activation parallels the increment of CD11A and CD11B levels in PD and Alzheimer's disease [30,31]. In another study, no change in the amount of TNF-α in PD specimens was observed, whereas IL-1β and IL-6 were elevated by 185% and 241%, respectively, exhibiting the highest amount of cytokine increase in the brain [32].

Oxidative stress refers to the imbalance between production and elimination of reactive oxygen species (ROS) and plays a major role in the pathogenesis of PD [3]. Several enzymes, such as those belonging to the cytochrome P450 family, cyclooxygenases, lipoxygenase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and xanthine oxidoreductases, are possible sources of ROS generation [33]. Oxidative stress occurs upon failure of the antioxidant defense system to eliminate excess ROS [34]. In normal physiological conditions, ROS are important mediators in various cell signaling pathways [35]. However, when this balance is disrupted, ROS compromise cellular functions, resulting in peroxidation of macromolecules and cell death [36].

3. Connexins

As much as 20 connexin (Cx) proteins have been characterized in mice and human. They are named according to their molecular weight as predicted by cDNA sequencing. [37]. Several genetic diseases, such as skeletal abnormalities, skin problems, hearing disorders and neuropathies, are associated with mutations in connexin genes [38].

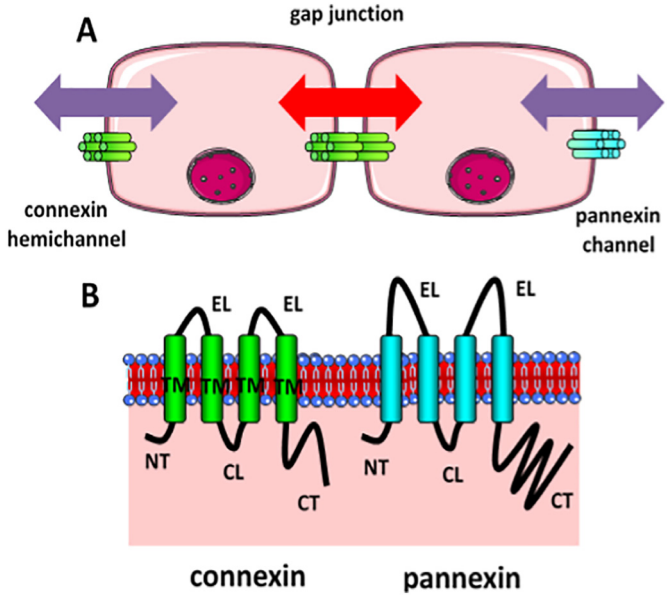

Fig. 1. A. *Architecture of gap junctions, connexin hemichannels and pannexin channels*. Gap junctions are formed by the interaction between 2 connexin hemichannels of adjacent cells and mediate intercellular communication (red arrow). Connexin hemichannels and pannexin channels are built up by 6 connexin proteins (green) and 6 pannexin proteins (blue), respectively, and support paracrine communication (purple). B. *Topology of connexin and pannexin proteins*. Connexin (green) and pannexin (blue) proteins all consist of 4 transmembrane domains (TM), 2 extracellular loops (EL), 1 cytosolic loop (CL), and 1 carboxy terminal cytosolic (CT) and amino terminal (NT) tail. In comparison with connexin proteins, pannexin proteins have longer EL and CT areas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Connexins have the ability to form hexameric membrane channels in unopposed cells known as hemichannels [39]. Connexin hemichannels of adjacent cells can dock to form gap junctions, which facilitate intercellular communication. In recent years, evidence has been accumulating showing that connexin hemichannels on their own can also provide a pathway for communication, albeit between the cytosol of an individual and its extracellular environment. Connexin hemichannels have been shown to play an important role in several pathological conditions [40,41].

The structure of connexins consists of 4 transmembrane segments (M1-M4), a cytoplasmic loop, 2 extracellular loops, a carboxy terminal tail and an amino terminal tail (Fig. 1). Differences between the connexin family members are mainly due to variations in the cytoplasmic loop and the carboxy terminal, while other parts are highly conserved. Connexins are expressed in a cell type-specific way [8]. Since various tissues express > 1 connexin type, homotypic (*i.e.* consisting of 2 identical hemichannels), heterotypic (*i.e.* composed of dissimilar hemichannels), homomeric (*i.e.* formed by only 1 connexin isoform) or heteromeric (*i.e.* containing different connexin isoforms) gap junctions may occur. Pore conductivity, charge selectivity, chemical and voltage gating of gap junctions and connexin hemichannels depend on the combination of the constituting connexins. Posttranslational alterations of connexins, such as phosphorylation, acetylation, methylation and ubiquitination, mediate the gating of the channels. Gap junctions are relatively non-selective channels and allow the passage of small (< 1 kilodalton) and hydrophilic molecular and ions [42].

Major connexins expressed in the CNS are Cx32 and Cx43, amongst others (Table 1). Cx43 is mainly harbored by astroglia and its channels are 8-fold more permeable to adenosine monophosphate and diphosphate, with a 300-fold higher permeability for adenosine triphosphate (ATP) than Cx32. In contrast, Cx32 expressed in oligodendroglia is 10-

Table 1
Expression of connexins and pannexins in the CNS.

	Cell type						
	Neuron	Astrocytes	Microglia	Oligodendrocytes	Endothelial cells	Oligodendroglia-astroglia gap junctions	Neuron-glial gap junctions
Connexin	Cx30.2 Cx31.1 Cx32 Cx36 Cx40 Cx45 Cx50 Cx57	Cx26 Cx30 Cx43 Cx40 Cx45	Cx32 Cx36 Cx29[a] Cx43[a]	Cx29 Cx32 Cx47	Cx37 Cx40 Cx43	Cx26-Cx32 Cx43-Cx47 Cx30-Cx32	Cx36-Cx45
Pannexin	Panx1 Panx2	Panx1 Panx2[b]	Panx1	Panx1 Panx2	Panx1 Panx2		

[a] Expressed in activated microglia, but not in resting microglia.
[b] *De novo* expression in reactive hippocampal astrocytes following ischemia/reperfusion injury.

fold more permeable to adenosine in comparison with Cx43 [43]. Cx29, Cx32 and Cx47 are expressed in the oligodendroglia of the CNS [44]. Cx29 mainly forms hemichannels. Cx32 and Cx47 can form homomeric, but not heteromeric gap junctions. Cx43, Cx26 and Cx30 are expressed in astroglia [45]. Cx43 can only give rise to homomeric gap junctions, while the other 2 connexin proteins can form homomeric and heteromeric channels. The combinations of Cx26-Cx32, Cx43-Cx47 and Cx30-Cx32 are mainly found in oligodendroglia-astroglia gap junctions, which are important in the transmission of calcium waves and metabolites as well as spatial buffering of the extracellular milieu [45]. Cx36 is the most widely expressed connexin species in mammalian neurons, mainly forming homomeric gap junctions, and is implicated in the current of electrical synapses in the brain [46]. Cx45 is similar to Cx36 in both expression site and activity. Cx36-Cx45 heterotypic channels are thought to be responsible for neuron-glial interactions [47,48]. Nonetheless, electron microscopy results support the idea that neuron-glia gap junctions do not exist [49]. Expression patterns of connexins in microglia, as critical constituents of the innate immune system in the CNS, is dictated by their activation status. Cx32 and Cx36 are connexins expressed in resting microglia cells, while Cx29, Cx32, Cx36 and Cx43 are the predominant connexin family members in activated microglia [50]. Also, microglia can regulate the expression of connexins and the activity of connexin hemichannels in astrocytes. It has been shown that TNF-α and IL-1β secreted from activated microglia influence the expression of Cx43 in astroglia [50]. Furthermore, activated microglia induce astroglial Cx43 expression, which has been linked to activated T cells [51]. ATP is an important communicative mediator between microglia and astroglia. The liberation of ATP from astroglial Cx43 hemichannels activates purinergic receptors on microglia. Subsequently, activated microglia boost glutamate release through Cx43-Cx32 hemichannels, which burgeons into neural injury [50].

4. Pannexins

Pannexins (Panx) are another group of communicating proteins in mammalian cells [52]. Their architecture is similar to that of connexins (Fig. 1). Pannexins are found in most cell types [53]. Pannexins have distinct roles in several physiological and pathological events, such as cellular proliferation, differentiation, migration, inflammatory responses, cytokine release, muscle contraction, glucose uptake in insulin-activated adipocytes and modulation of the neural system [54]. Panx1, Panx2 and Panx3 are the only 3 known members of the pannexin family [55]. The presence of glycosylated asparagine residues in the extracellular domains of pannexins prohibits intercellular channel (*i.e.* gap junction) formation. Rather, pannexins form hexameric channels in the cellular membrane reminiscent of connexin hemichannels. Many factors, such as inflammation, cytotoxicity, extracellular ATP release, glutamate, and elevated intracellular calcium concentration, can open pannexin channels [56,57]. The messengers that travel through pannexin channels are very similar to those involved in connexin hemichannel and gap junction communication. Interaction of Panx1 with purinergic receptors (P2X7) leads to the liberation of ATP and IL-1β [58].

As holds for connexins, mutations in the genes that encode pannexins have been associated with disease. Patients with Panx1 gene mutations show several problems in many organs and tissues such as hearing loss, premature ovarian failure and skeletal defects [59]. Panx1-null mice have revealed the role of pannexins in the protection against ischemic stroke damage, regulation of neural excitability, narcotic withdrawal, and learning [60–63].

5. The role of connexins and pannexins in PD

Non-neuronal cells, like astrocytes, play a pivotal role in the degeneration of dopaminergic neurons [64]. The level of extracellular concentrations of glutamate and potassium as well as pH in astrocytes is maintained by Cx43 [6,65]. It has been shown that Cx43 expression is elevated in a rotenone-induced model of PD. Rotenone is a common pesticide that blocks mitochondrial complex I and that increases Cx43 expression in cultured astrocytes, resulting in enhanced gap junctional communication [6]. This coincides with an increase of Cx43 phosphorylation both *in vitro* and *in vivo*. This mainly occurs in the basal ganglia region of the brain, which encompasses dopaminergic neurons. However, the substantia nigra pars reticula shows higher levels of Cx43 in comparison with the substantia nigra pars compacta. Thus, modulation of astroglial Cx43-based gap junctional communication might play an important role in the pathogenesis of PD [12]. Cx30 is upregulated in astrocytes in the striatum of PD brain samples. Also, Cx30 knock-out mice display elevated loss of dopaminergic neuron and attenuated astrogliosis after PD induction, while no change is observed in microglial function. Hence, Cx30 may be involved in the protection of astrocytes against PD [66].

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is another neurotoxic substance known to induce parkinsonism *in vivo*. However, the administration of MPTP to mice does not trigger adequate loss of dopaminergic functions. Co-administration of MPTP with the clearance inhibitor probenecid, which also acts as a Panx1 channel blocker, results in significant loss of striatal dopamine for at least 6 months [67]. It has been reported that total astroglial Cx43 mRNA quantities and Cx43-immunoreactive gap junction plaques increase in MPTP-treated mice. However, this is not accompanied by enhanced functional coupling [68]. In fact, the striatum of MPTP-treated mice shows an abundance of basal fibroblast growth factor (FGF), which is a powerful trophic protein for mesencephalic dopaminergic neurons. Likewise, exogenous administration of FGF stimulates Cx43-positive gap junction plaque formation, yet does not increase gap junction coupling in murine

astrocytes [68]. The discrepancies in induction of gap junctional coupling throughout these studies might be related to differences between MPTP and rotenone models of PD.

There are very few data about the role of Panx1-based channels in the activity of astrocytes and neurons in PD. The upregulation of FGF in the striatum of MPTP-treated mice has been well accepted [69]. Despite the trophic function of FGF1 in dopaminergic neurons, it may modulate Panx1 channels leading to damaging cellular events [70]. Using an *in vitro* model of spinal cord injury, it was found that a feedback loop occurs in spinal cord astrocytes in which FGF receptors are activated by FGF1, resulting in vesicular ATP liberation. Released ATP induces purinergic P2X7 receptors in a feedback system, which in turn activates Panx1 channels in astrocytes that secrete ATP. This autocrine feedback loop actives Cx43 hemichannels, which exacerbate the release of ATP from astrocytes [70]. The presence of excess ATP in the extracellular space generates a sustained inflammatory condition that might influence resident neurons and glial cells in a negative manner [70]. A parallel mechanism involving Panx1 channels and FGF1 might also take place in the striatum in PD [71]. P2X7 receptors act as important targets of endogenous ATP in astrocytes in physiological conditions. Upon activation, these receptors initiate the release of signaling molecules from astrocytes, which stimulates neighboring neurons. Outward passage through P2X7 receptors solely or in association with Panx1 channels is proposed to be a plausible mechanism of liberation of signaling molecules by astrocytes. During neurodegenerative disease, including PD, microglial P2X7 receptors are activated in response to the large concentrations of ATP [72–74]. In a next step, several cytotoxic mediators, such as glutamate, ROS and excess ATP, are secreted by activated microglia, ultimately resulting in cell death [75].

Accumulation of α-synuclein is another hallmark of PD that has been linked to communicating proteins. The enhanced opening of astroglial, neuronal and glial connexin hemichannels is believed to coincide with a drop in gap junctional coupling in PD. Gap junctional communication in dopaminergic neuroblastoma cells is diminished because of overexpression of α-synuclein. Subsequently, these cells become more susceptible to any toxic condition [76]. Furthermore, Cx32, which is expressed in the substantia nigra, binds to α-synuclein [77]. The liberation of α-synuclein in the extracellular space is a triggering factor in the propagation of brain neurodegeneration in PD [78]. It has been demonstrated that P2X7 receptors mediate extracellular α-synuclein toxicity [79]. In addition, exogenous α-synuclein can activate P2X7 receptors in neuroblastoma cells, which activate Panx1 channels to release ATP, resulting in neurotoxicity [79].

The occurrence of neuronal apoptosis in the substantia nigra pars compacta has been proposed to be a crucial mechanism of PD pathogenesis. To elucidate the apoptotic mechanism in PD, 1-methyl-4-phenylpyridine (MPP+) has been used for induction of cell death in the dopaminergic SH-SY5Y cell line [80]. MPP+ is a well-known PD inducer or parkinsonian toxin that interferes with oxidative phosphorylation in mitochondria. SH-SY5Y cells, devoid of Cx43 by short hairpin RNA knockdown, showed enhanced apoptosis upon treatment with MPP+ associated with a decreased Bax/Bcl2 ratio and cytochrome *c* release. Thus, Cx43 could act as a neuroprotective factor in the prohibition of the mitochondrial apoptosis cascade in SH-SY5Y cells after treatment with a parkinsonian toxic substance [80,81].

The chronic inflammatory response and increased expression of Cx43 in PD as well as in other neurodegenerative diseases suggest that modulation of connexin expression might offer therapeutic opportunities by interfering with the inflammatory cascade [22,82]. In this respect, the activity of astrocyte glucocorticoid receptors in GRCx30CreERT2 mice was investigated in a MPTP model of PD. These mutant mice with inactivated glucocorticoid receptors exhibit increased dopaminergic neurons loss in the substantia nigra. Furthermore, microglial activity is increased in these mice, but not astrocytes. However, production of inflammatory proteins, including intercellular adhesion molecule 1 (ICAM-1), TNF-α, and Il-1β, was upregulated in astrocytes. This event was concurrent with increased connexin hemichannel activity and enhanced calcium concentrations in astrocytes. *In vivo* studies performed in parallel also showed enhanced Cx43 quantities in a PD mouse model. Moreover, *postmortem* studies of PD patients revealed a substantial decline in the number of glucocorticoid receptor-expressing astrocytes, thereby proposing a distinct role of astrocytic deregulation of the inflammatory cascade in PD [83].

It has been reported that Cx37 and Cx45, like Cx43, are highly expressed in PD, whereas Cx26 and Cx25 are downregulated. Vascular leakage and enhanced endothelial cell coupling have been associated with enhanced expression of Cx37, Cx43 and Cx45 in brain endothelial cells in PD [84,85]. Since PD goes hand in hand with the occurrence of astrocytosis and gliosis, an increase in production of connexins in astrocytes and microglial cells is predicted [32]. Cx43, as the most prevalent connexin variant in inflammatory conditions, has been shown to be upregulated in PD [22,86]. Microglial activation leads to the release of inflammatory mediators that disturb blood vessels and instable capillaries. In addition, activated microglia increase connexin hemichannel opening, resulting in an upward trend in a bidirectional exchange between the intracellular and extracellular compartments [87,88].

It has been demonstrated that Cx47 and Cx32 are downregulated in PD, yet Cx30.2 remains unchanged. These 3 oligodendrocytal connexins have been causally linked with demyelination in neurodegenerative disease [89,90]. Cx31.9, which is expressed in the cerebral cortex, was also found to be downregulated in PD [91].

A body of evidence has supported the role of pannexins in oxidative stress, which is an important mechanism of toxicity in PD. Panx1 channels have been shown to induce the production of ROS [92]. Also, extracellular ATP-mediated ROS formation has been attributed to the activity of P2Y1 receptors during electrical stimulation in skeletal muscle cells [93]. On the other hand, oxidative stress itself can stimulate pannexin channels. It has indeed been demonstrated that ROS augment the activity of Panx1 channels during oxygen/glucose deficiency in a hippocampal neuron ischemia/reperfusion model [94]. This suggests that there is a close relationship between oxidative stress and Panx1 channels. Their interaction is a vital phenomenon in normal physiological conditions or during the progress of oxidative stress-related disorders, yet the precise mechanism remains unknown. The generation of ROS in hippocampal neurons is controlled by the function of P2Y receptor-activating nucleotides [95]. ATP-stimulated activation of P2Y2 receptors is crucial for mechanical stress-related calcium influx [96]. While oxidative stress increases calcium influx, ROS homeostasis is maintained through calcium signaling [97,98]. Therefore, activation of pannexin channels through ATP release is suggested to be involved in oxidative stress-related disease, including PD, *via* the accumulation of ROS as a result of calcium influx. Low potassium concentration as well as the presence of excess ROS activates NLRP3 inflammasomes. The latter control the release of IL-1β and IL-18. It has been reported that NLRP3 inflammasome activation is inhibited by Panx1 channel blockers, thus suggesting a role for Panx1 in the inflammatory cascade [99]. NLRP3 inflammasomes indeed play key roles in the pathogenesis of PD. Increased activation of NLRP3 inflammasomes in brain microglia is observed following induction of PD *in vivo*. *Vice versa*, administration of an inhibitor of the NLRP3 inflammasome reverses motor performance, neurodegeneration and neuro-inflammation in a mouse model of PD. This effect coincides with a decrease in the accumulation of α-synuclein in the brain [100]. A critical downstream effector of the NLRP3 inflammasome includes capase 1. Administration of the caspase 1 inhibitor Ac-YVAD-CMK was found to alleviate PD symptoms in a lipopolysaccharide-induced mouse model [101].

Despite the acknowledged role of Panx1 in NLRP3 inflammasome activation, its channel opening is self-regulatory and blocked by an excess of extracellular ATP. Therefore, connexin hemichannels are more likely to maintain the chronic phase of PD (Fig. 2). It has been shown that inflammatory conditions trigger Panx1 channel opening. In

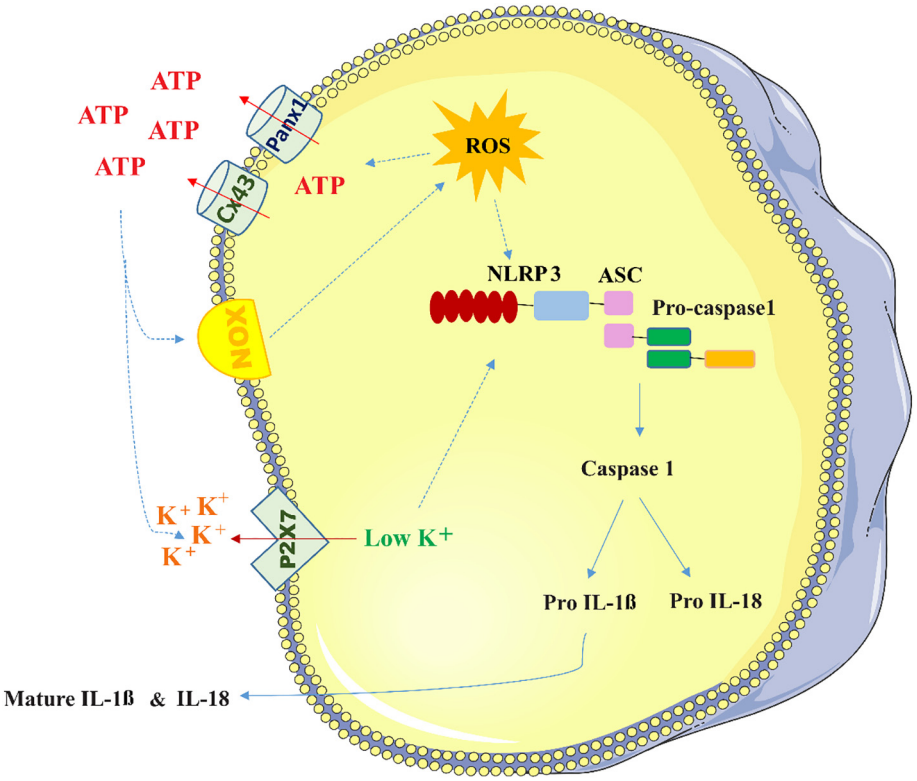

Fig. 2. *Involvement of pannexin channels in the pathogenesis of PD in context of oxidative stress.* Intracellular ROS activate Panx1 channels, which leads to the release of ATP. This, in turn, stimulates the activity of P2X7 receptors resulting in both potassium efflux and NADPH oxidase activation, which generates ROS. In addition, the opening of Panx1 channels coincides with the activation of NLRP3 inflammasomes and further release of inflammatory cytokines. The dashed arrows represent stimulatory effects.

addition, connexin hemichannels are activated in response to the increased resting calcium levels in Alzheimer's disease [4]. The activation of NLRP3 inflammasomes and other signaling pathways following activation of connexin hemichannels might place neural cells in the center of a voracious circle in PD. Hence, blocking the activity of connexin channels could represent a surrogate therapeutic strategy in PD.

Formation of neuritic beading as an initial pathologic feature of excitotoxicity is a common hallmark of neurological disease, including PD [102]. Microglial glutamate has been shown to play a fundamental role in the formation of neuritic beading and subsequent cellular events *via* activation of neuronal *N*-methyl-D-aspartate receptors. This boosts calcium influx and calcium/calmodulin-dependent protein kinase (CaMK) activation. CaMK increases the level of intracellular nitric oxide (NO) through activation of nitric oxide synthase. Subsequently, NO rapidly reduces intracellular ATP concentrations by inhibition of mitochondrial respiratory chain complex IV. Deprivation of cellular ATP reservoirs compromises dendritic and axonal transport, which results in the build-up of cytoskeletal and motor proteins and concomitant generation of neuritic beads. This will ultimately lead to neuronal death [103]. Glutamate production by activated microglia relies on 2 pathways [104]. In a first pathway, α-ketoglutarate is converted to glutamate through the actions of glutamate dehydrogenase. The majority of cells preserve their glutamate levels within this pathway. Glutamate could also have an extracellular origin *via* the action of glutamine transporters and the enzymatic activity of glutaminase in the second pathway. Physiological glutamate levels are maintained through the first pathway in resting microglia. By contrast, activated microglia generate excessive amounts of glutamine through upregulation of glutaminase. In a further step, connexin hemichannels secrete glutamate. The release of inflammatory cytokines increases the localization of connexin hemichannels in microglia and elevates glutaminase expression [105,106]. The synergistic effect of these 2 processes collectively triggers the excitotoxicity impact of excess glutamate [107] (Fig. 3).

6. Gap junction inhibitors in PD modulation

A plethora of chemicals has been reported to act as gap junction blockers (GJBs). However, these compounds are usually not selective and can bind to many other targets, which may result in quite pleiotropic effects [108]. A number of GJBs have been introduced for application in PD. Beta oscillations in basal ganglia of PD animal models and parkinsonian patients is a common feature of the disease, which is linked with gap junction activity. Electrophysiological studies have shown the role of GJBs in the attenuation of beta oscillatory activities occurring in the globus pallidus in hemiparkinsonian rats. Carbenoxolone (CBX) and octanol, which are well-known GJBs, significantly diminish beta oscillations and improve forepaw akinesia in a PD rat model [109]. CBX is a water-soluble derivate of glycyrrhetinic acid that can also inhibit 11β-hydroxysteroid dehydrogenase [110]. It has been shown that CBX can equally suppress the activity of Panx1 and Panx2 channels, P2X7 receptors as well as of Cx38-based and Cx26-based gap junctions [111–113]. CBX has shown promising effects in protection against PD [17]. Furthermore, CBX was found to reduce α-synuclein accumulation in a rotenone-induced model of PD [114]. This effect parallels the reduction of inflammation and mitochondrial injury related to the aggregation of α-synuclein, which is partly due to the blocking effects of CBX on Cx43 gap junctions and Panx1 channels [17].

Tonabersat is a *cis*-benzopyran compound with inhibitory effects on connexin hemichannels. It has been reported that tonabersat reduces Cx26 expression in the brain through inhibiting the p38-mitogen activated protein kinase cascade. Furthermore, it can directly bind and block Cx43 hemichannels. Tonabersat has been demonstrated to shut down ATP liberation mediated by Cx43 hemichannels in a model of ischemia/reperfusion. Tonabersat has been formerly used in clinical trials for the treatment of migraine and is proposed to be an effective connexin hemichannel blocker in the therapy of neuro-inflammatory disorders [115].

Anesthetics, such as ketamine, propofol and dexmedetomidine, significantly block gap junctional communication between astrocytes *in vitro* [116]. Gastrodin, a component of a Chinese herbal medicine, has

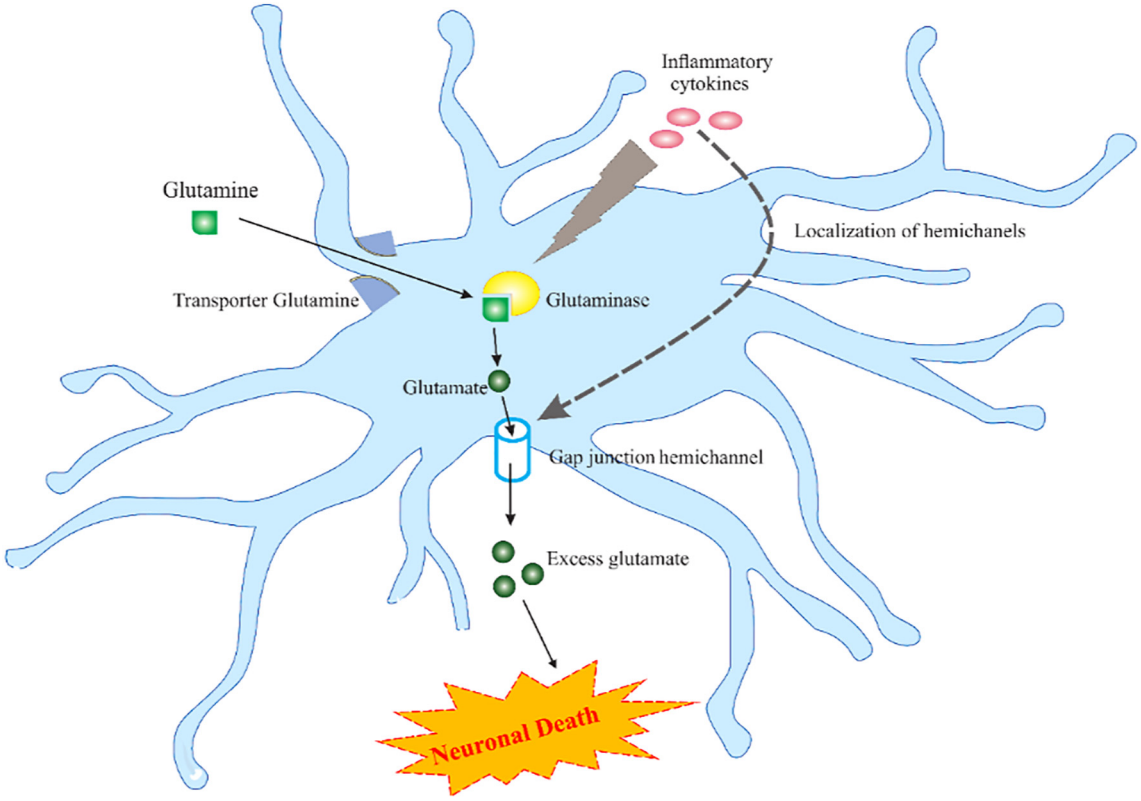

Fig. 3. *Mechanism of glutamate production and release by activated microglia.* The upregulation of glutaminase, which enhances intracellular levels of glutamate in activated microglia, is mediated *via* the activity of inflammatory cytokines. These cytokines support increased presence of connexin hemichannels in microglia, which transport the excess glutamate resulting in neuronal death.

also been used as a GJB. The expression of Cx43, its phosphorylation and associated cell coupling all are negatively affected by gastrodin in a rotenone-induced PD model in rat [78]. Importantly, gastrodin counteracts the clinical manifestation of PD in this experimental model [117]. The reduced expression of Cx43 by gastrodin could affect Cx43 hemichannel activity, which may account for the beneficiary outcome [71].

Cannabinoids (CBs) have been proposed as potential therapeutics in the treatment of neurodegenerative diseases. Inflammation and degeneration lead to an increase in brain endocannabinoids and glial CB receptors, which are implicated in the neuroprotective effects of endogenous CBs. Recent evidence has shown that CBs are important substances to counter uncontrolled opening of connexin hemichannels and pannexin channels in neuro-inflammatory situations [118,119]. It has been proposed that endocannabinoids inhibit the stimulation of main inflammatory pathways that control the production of cytokines, being important instigators of astroglial connexin hemichannel activation [120]. CBs also exhibit neuroprotective effects *via* alteration of gap junctional communication in neural tissues. For instance, anandamide, which is an endogenous arachidonic acid derivate, can activate neural CB receptors through inhibition of gap junctional conductance in astrocytes [121]. CB agonists not only inhibit lipopolysaccharide-induced release of inflammatory cytokines from microglia, but also reverse Cx43 function in pro-inflammatory conditions leading to neural survival [122]. Moreover, CBs prevent inflammation-induced astroglia connexin hemichannel activation, which can result in neural death [123].

Probenecid as a well-known inhibitor of organic anion transporters has been shown to block Panx1 channels in a concentration-dependent manner. Interaction with the extracellular loop of Panx1 is considered to be the mechanism of action, which is similar to the function of CBs. Probenecid also inhibits human P2X7 channels as shown by patch-clamp and calcium indicator studies [8].

Most connexin drug delivery approaches have been focused thus far on Cx43. Cx43 is indeed recognized as an early responder to many kinds of injuries [124]. However, there is a need for approaches to determine how and where in its life cycle Cx43 could be targeted. Furthermore, specific inhibitors of the different channels types, in particular Cx43 gap junctions *versus* Cx43 hemichannels, as well as cell type-specific inhibitors are urgently required. Antibodies raised against specific parts of Cx43 seem promising in this respect [125].

7. Conclusions and perspectives

Knowledge of the CNS and peripheral nervous system and related diseases is increasing rapidly. In this manuscript, a brief overview was presented regarding our current neuropathological and molecular understanding of PD treatment. The reviewed literature showed the critical roles of connexins, pannexins and their channels in the regulation of the CNS/peripheral nervous system both in physiological and pathological conditions. Studies have verified their functions as drug targets for the development of new therapies of PD. Connexin-based and pannexin-based cellular communication exerts distinctive functions and is indispensable for securing homeostasis in the CNS. Perturbation of the neuroglial network results in severe systemic dysfunction. Given the role of connexins, pannexins and their channels in the pathogenesis of PD and the evidence of the protective role of their inhibitors, the modulation of these channels as potential targets of PD is warranted. GJBs have shown promising effects in this context. It should, however, be mentioned that the production and testing of such specific channel inhibitors is challenging for many reasons [8]. Furthermore, more studies are needed to focus on the development of stable, effective and specific modifiers of connexin hemichannels, gap junctions and pannexin channels. In addition, more insight into their function as drug targets for the development of new treatments for PD disease is

required. Cutting-edge animal models will help to clarify the roles of these channels in normal and pathological situations in CNS-related diseases. Clinical trials with exact thought-out step-by-step processes will give comprehensive consideration of these systems and will provide critical data for the establishment of novel PD treatment methods.

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Conflict of interest

The authors have no conflict of interest to report.

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