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## Chapter

# Mitochondrial $K_{ATP}$ Channel and Dopaminergic Vulnerability Neurons in Parkinson's Disease

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## Abstract

The motor deficiency control commonly characterizes Parkinson's disease (PD), resulting in impairment of neuromuscular command, because of basal ganglia nuclei degeneration and late formation of Lewy's bodies in the remaining dopaminergic (DA) neurons. Motor signals are triggered in high cortical motor areas and go toward the midbrain regions, where the final tuning movement takes place. PD is characterized primarily by the death of dopaminergic neurons in the regions known as *substantia nigra compacta* (STNc). Mutations in a couple of genes, such as Parkin1 and DJ1, correspond to the usual familial form of the disease, due to its association with oxidative stress and depolarization of mitochondrial membrane. However, this form does not explain the selective pattern of apoptosis between the neuronal dopaminergic areas of midbrain regions. In this chapter, we are putting forward the hypothesis of oxidative stress and mitochondrial changes as the apparent most relevant cause in PD, as well as the neuroprotective role played by Kir6.2, a potassium-ATP channel and calcium voltage-gated v1.3.

**Keywords:** Parkinson's disease, potassium- $_{ATP}$  channel, calcium v1.3 channel, mitochondria ETC impairments, oxidative stress

## Glossary:

1. PD nonhuman animal model: simulation of PD may be acquired using rotenone and MPTP, two pesticides whose use leads to impairments in mitochondrial complex-I and in consequence an outburst of oxidative species and free radicals.
2. Kir6.2/SUR1: during oxidative stress, potassium-ATP channel may act as a neuroprotector factor, by inducing GABA release in subcortical areas, thereby preventing neuronal glutamatergic overexcitation.

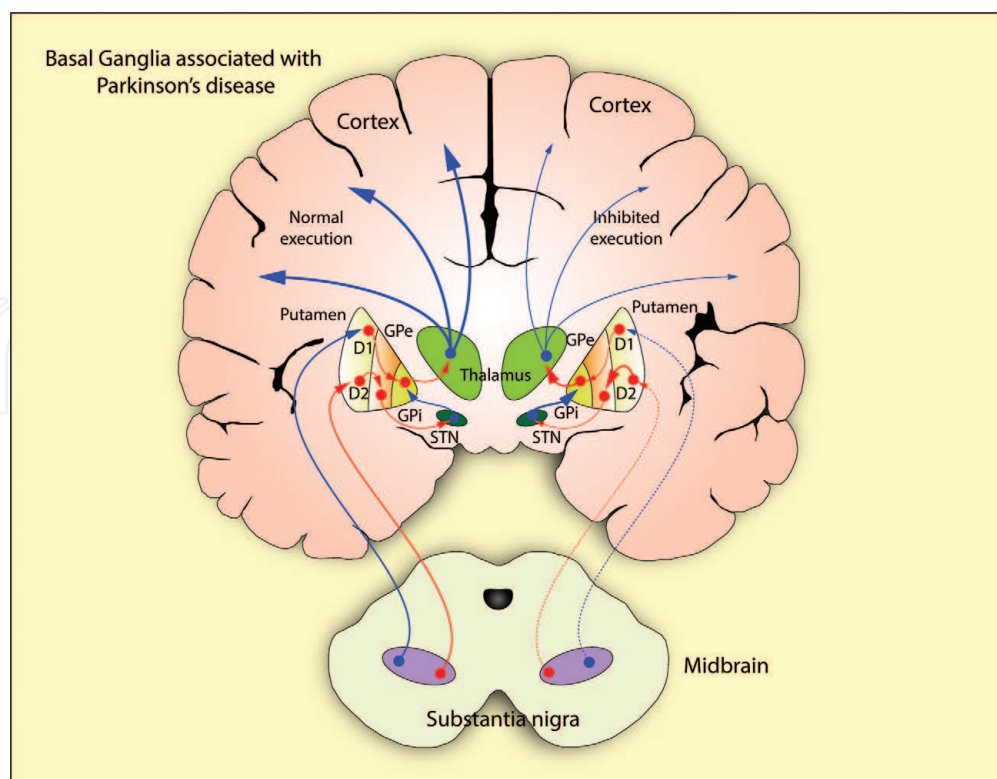
## 1. Introduction

Parkinson's disease (PD) is related to the selective loss of neurons, which contain dopamine (DA) in *substantia nigra compacta* (STNc) and late formation of Lewy's bodies in the remaining dopaminergic (DA) neurons [1]. PD is one of the most conditions, falling behind only Alzheimer's disease. Parkinson's disease prevalence is progressive, ranging from 1% in people >60 years old until 2–4% in people >70 years old.

PD is commonly known by the disease of the motor deficiency process [2]. Due to its association with impairments in basal ganglia, the presence of resting tremor, muscular rigidity, bradykinesia, sleep disturbances, gait impairment, and difficulties with balance [3–5] became the most prominent footprint in PD characterization (see **Figure 1**) [4].

In humans, movements are coordinated by a series of high-precision steps that begin in the regions of the prefrontal cortex and go toward the areas directly related to movement coordination, such as supplementary area and primary motor area [6]. From the start point, the signal follows pathways from inside the brain into the sub-cortical regions and reaches the spinal cord and finally the skeletal muscle [7]. However, it is not enough to simply generate the motor signal and deliver it to the muscle; it is necessary to coordinate and control the accuracy of the process generated in high cortical regions. That is the point where basal ganglia take place on this process as a stakeholder (**Figure 1**) [8].

Basal ganglia are composed of a series of subcortical nuclei scattered for the midbrain regions, whose role extends from the motor fine-tuning, initialization, and finalization of the movement (processes supported by the *substantia nigra pars compacta* (STNc)), as well as the development of cognitive functions such as learning, reward, and emotions, mostly supported by the ventral tegmental area (VTA) and

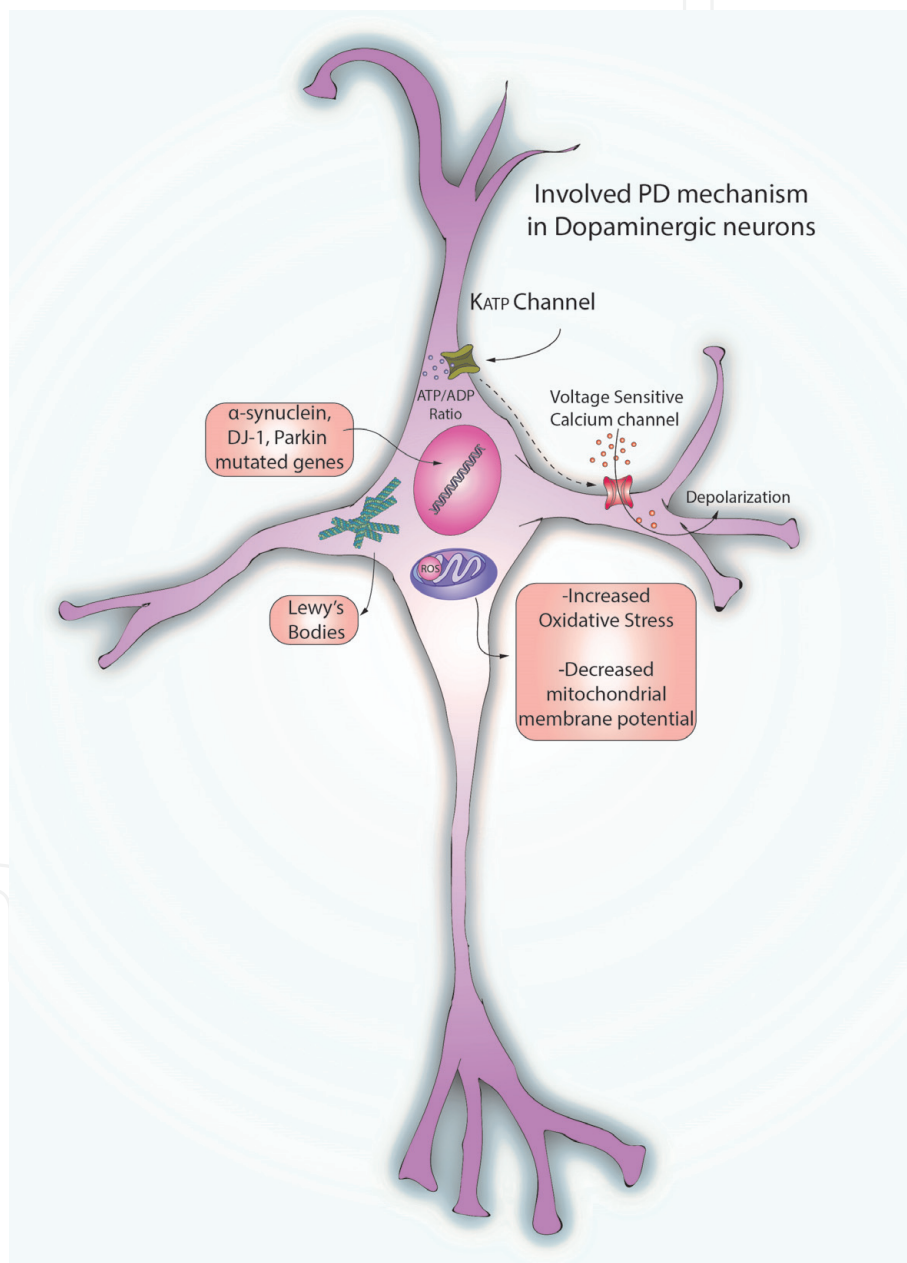


**Figure 1.** The basal ganglia and a series of subcortical nuclei responsible for the motor fine-tuning in health brain (right) and in PD (left). Direct pathway provides the disinhibition of the thalamus (D1 signaling in blue). Indirect pathway, in red, will stop the movement, previously initiated. D1, dopamine receptor 1; D2, dopamine receptor 2; GPi, globus pallidus internus; GPe, globus pallidus external.

nucleus *accumbens* (NC). Together, they are functionally known as the ventral and dorsal *striatum*, respectively [9].

As one can see in **Figure 1**, in parkinsonism, the striatum plays an important role in the pathophysiology of the disease, and the substantia *nigra* compacta (STNc) emerges as the main nucleus responsible for the core mechanism related to the initialization of the movement, assigned to the direct pathway [10]. Direct pathway provides the disinhibition of the thalamus by the dopamine D1 signaling, performed by STNc [11]. In opposite side, the indirect pathway will stop the movement, previously initiated by the release of GABA from the external *globus pallidus* (GPe) and *substantia nigra pars reticulata* (STNr) [12].

James Parkinson did the first description of the disease in 1817 in his book: *An Essay on the Shaking Palsy* [13]. PD is characterized primarily by the death of

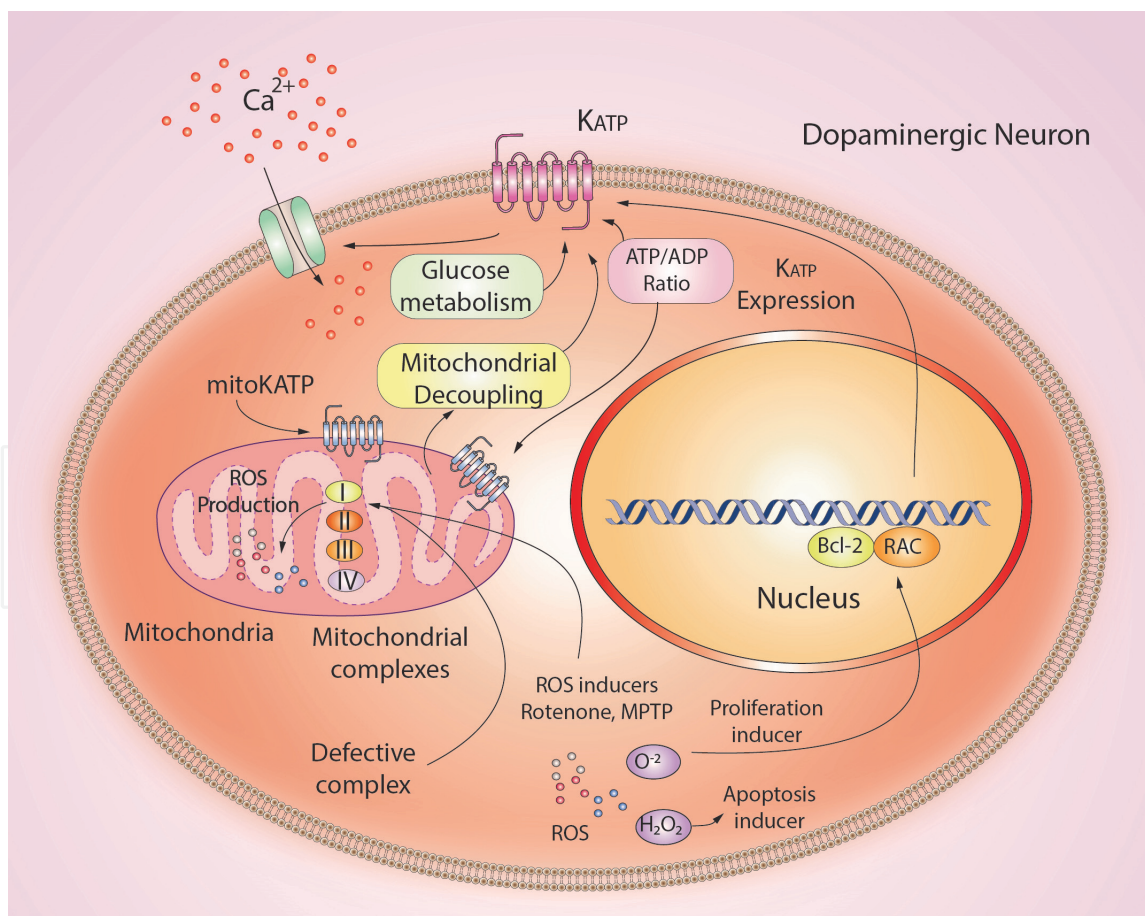


**Figure 2.** Dopaminergic neurons undergo several mechanisms that may explain in part the selective cell death in substantia nigra. Mutations associated with major PD related genes such as  $\alpha$ -synuclein, DJ-1 and Parkin are well characterized. It is possible that the mutated genes induced a protein imbalance that lead to the aggregation of proteins to form the so-called Lewy's bodies. Another key mechanism studied is the ROS imbalance in mitochondria resulting in a diminished ATP that affect the ability of dopaminergic neuron to reach its main functions. A plausible mechanism to be explored is the role of K-ATP channel that is sensitive to ATP/ADP changes to govern the depolarization in GABAergic neuron.

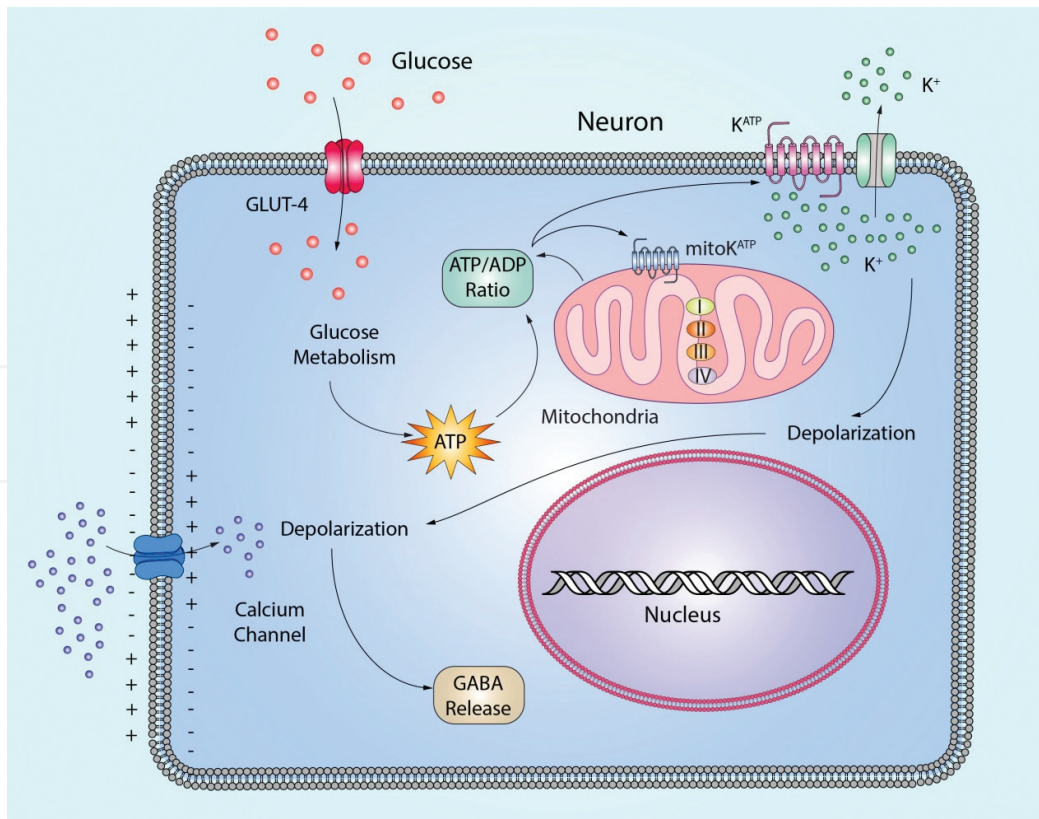


dopaminergic neurons in the STNc resulting in defective control of the movements in the basal ganglia (**Figure 1**) [14]. However, in addition to dopamine metabolism impairment, another pathological process implicated in the etiology of the disease is the aggregation of alpha-synuclein (a-syn), resulting in Lewy's body formation in the remaining dopaminergic neurons, characterizing the non-motor symptoms of the disease (**Figure 2**) [4, 5, 15].

Despite the dominant prevalence of sporadic form (90%), mutations in genes, such as a-synuclein, DJ1, Parkin1, and others, have been implicated in the familial pattern of PD, mainly due to their associations with oxidative stress responses and depolarization of mitochondrial membrane. However, gene alterations in the familial form of PD are ambiguous because they do not explain the selective pattern of apoptosis between STNc and VTA, both formed predominantly by dopaminergic neurons (**Figure 2**) [14, 16]. Another hypothesis associated to the oxidative stress and mitochondrial changes is related to  $Ca^{2+}$  imbalance homeostasis in dopaminergic neurons of the STNc, as well as the presence of  $K_{ATP}$  channels acting as a metabolic sensor by coupling glucose metabolism to mitochondrial membrane potential (Mit- $\psi$ ) (see **Figures 3** and **4**) [17]. In other words, understanding the mechanism of specific vulnerability, by which only dopaminergic neurons in specific areas are associated with PD, remains an impressive challenge; however, some evidences, that will be discussed here, may shed light in an intricate neurobiology of Parkinson's condition [14, 18].



**Figure 3.** *K-ATP and mitochondrial functions may be a potential relationship. K-ATP sensor is subjected to regulation via several mechanisms as glucose metabolism, ATP/ADP ratio, mitochondrial decoupling, and gene expression. K-ATP may lead the neuron to depolarize via potassium and calcium fluxes. It is reported that K-ATP has other subtypes of receptors, for example, the mito- $K_{ATP}$ . It is possible that the pathogenic production of ROS may alter the function of K-ATP with protective functions. So, it is plausible that the modulation of K-ATP receptors can be used to protect dopaminergic neurons.*



**Figure 4.** Glucose and energetic metabolism may regulate the function of  $K_{ATP}$  channel. The change in the ATP/ADP ratio by glucose metabolism induces a response in  $K_{ATP}$  that blockade the potassium outward with the subsequent loss of membrane potential. It may lead to depolarization with several functions, for example, the release of GABA.

## 2. Substantia nigra compacta and ROS formation

The use of rotenone and MPTP, two pesticides, which act on the mitochondrial complex-I, brought mitochondrial damage induced by oxidative stress to the center of PD etiology. The uplift of reactive oxygen species (ROS), caused by a defective complex-I, such as observed in PD patients, makes mitochondria the main source of ROS in the intracellular environment (**Figure 3**) [19, 20]. Superoxide ( $O_2^-$ ) and peroxide of hydrogen ( $H_2O_2$ ), the two main species of ROS derived from electron transport chain (ETC) activity, seem to govern the internal state of the cell between proliferative and apoptotic. According to this model, high levels of  $O_2^-$  tend to favor cell proliferation due to increased transcription of oncogenes, such as the Rac1-Bcl2 pathway, whose overexpression increases mitochondrial respiration. On the other hand, prevailing levels of  $H_2O_2$  promote apoptosis, and finally, very high rates of  $H_2O_2$  promote cellular necrosis due to irreparable damage to cell physiology (**Figure 3**) [21].

The hypothesis of oxidative stress and mitochondrial changes is apparently the most relevant cause in the sporadic PD (**Figure 3**). However, they alone do not explain selective dopaminergic neuron vulnerability. The key element for this may lie in the differential expression of  $K_{ATP}$  channels (Kir6.2) between STNc neurons and ventral tegmental area (VTA) [22]. In *in vitro* studies, the total decoupling of the mitochondrial respiratory chain leads to the activation of  $K_{ATP}$  channels in all dopaminergic neurons. However, partial decoupling of complex-I strongly affects neurons from STNc, showing an opposite effect on  $K_{ATP}$  channels in dopaminergic neurons of VTA, whose process increases the neuronal activity, reducing ROS formation due to the closure of the  $K_{ATP}$  channels (**Figure 4**). It has been identified

that D2-autoreceptor (D2-AR) acts as an inhibitor of STNc-DA neurons in response to local high DA release [23]. All the processes have been achieved by activation of Kir6.2, an inward rectifier potassium channel coupled to G-protein [23]. Although ventral tegmental area DA neurons (VTA-DA) do not present the same response in such like condition [24], studies account for the presence of  $Ca_v^{+2}1.3$  channel as the main responsible for this selectivity in STN-DA neurons, whose function would be associated with the downregulation of STN-DA neuronal cell activity in response to dangerous transient of local DA release [25].

## **2.1 The starting point of oxidative stress and $K_{ATP}$ channel disposition**

In PD, pathogenesis predominates the selective loss of dopaminergic neurons. These neurons are in the STNc, with projections up to the striatum zone. The neurochemistry of degeneration involves several molecular events triggered by mitochondrial dysfunction with increased oxidative stress and excitotoxicity caused by extracellular  $Ca^{+2}$  overflow. These events promote important changes in protein conformation, e.g., alpha-synuclein, responsible for Lewy's body formation, a defective protein aggregation resulting in mitophagies and apoptosis [26–28].

Dopamine is a catecholamine synthesized from the L-dihydroxyphenylalanine (L-dopa) of the amino acid tyrosine by the enzyme tyrosine hydroxylase (TH). In the next step, L-dopa undergoes decarboxylation by the aromatic amino acid decarboxylase (AADC) to generate dopamine and  $CO_2$ . TH and AADC form a complex with the vesicular monoaminergic carrier-2 (VMAT-2), facilitating the uptake of dopamine in the monoaminergic synaptic vesicles [29]. The TH, the AADC complex, and the VMAT-2 transporter facilitate the absorption of dopamine in the monoaminergic synaptic vesicle, thus avoiding the oxidation of dopamine to o-quinones by the dissociation of the hydroxyls of the catechol present in the molecule when at p. 7.4 of the cytosol [30]. In the monoaminergic vesicle, the stability of the molecule in the protonated form is conferred by an estimated pH of approximately 5 [30].

Dopamine, which is not absorbed by VMAT-2, is transported freely by the cytosol and may undergo oxidation by monoamine oxidase to give rise to dihydroxyphenylacetic acid, methylation by ortho-methyltransferase, and structure oxidation of catechol to o-quinone aminochrome [31]. O-Quinones derived from dopamine to form aminochrome are rapidly mopped by cysteines (or other thiols present) generating forms that are oxidized to form melanotic pigments [32–34]. The action of flavenzyme FADH, such as DT-diaphorase induce the formation of hydroquinone and ROS from reduction of o-quinones derived of freely dopamine in the cytosol [35, 36]. Semiquinone is a highly reactive radical, and under aerobic conditions, it catalyzes the reduction reaction of oxygen to the superoxide that activates the redox cycle between the leucoaminochrome o-semiquinone radical and the aminochrome [37, 38].

Aminochrome leads to the formation of species with proteins of complexes I and III of the mitochondrial electron transport chain associated with reduced flavin adenine dinucleotide ( $FADH_2$ ) [39]. It forms compounds with the isocitrate dehydrogenase, leading to mitochondrial dysfunction due to a decreased ATP production [40]. In addition, aminochrome forms adducts with alpha-synuclein protofibrils and with Parkin leading to proteasome dysfunction, with actin leading to dysfunction in axonal and cytoskeletal transport, aggregation of  $\alpha$ - $\beta$  tubulins leading to autophagy dysfunction [41, 42]. In PD models, the active metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP),  $MPP^+$ , and rotenone are mitochondrial toxins that inhibit the NADH-quinone oxidoreductase complex respiratory [37, 43, 44].



## 2.2 Mitochondrial $K_{ATP}$ channels

Mitochondrial dysfunction seems to play a crucial role in PD [44–47]. Mitochondria is directly implicated in ROS generation and consequently in neuronal cell death in vulnerable population. Mitochondrial  $K_{ATP}$  channels (mito- $K_{ATP}$ ) act as a gate control linking metabolism with cell survival and neurotransmitter releasing (**Figures 2 and 4**) [48]. Kir6.2 mito- $K_{ATP}$  channels are encoded by KCNJ11 gene family, whereas SUR1, the  $K_{ATP}$  channel sensor subunit, belongs to the class of ABC8, a subfamily of membranes transporters [49, 50].

$K_{ATP}$  channels are triggered by the ATP/ADP rate, opening in response to reduced levels of ATP and, closing, otherwise, linking  $K_{ATP}$  channels in a direct relationship with the neuronal sugar metabolism and the action potential [51]. In physiological conditions, in dopaminergic neurons, these channels are probably closed. On the other hand, in PD model induced by MPTP administration in mice, the ATP depletion and mitochondrial dysfunction are observed, thus triggering the opening of the mito- $K_{ATP}$  channels (**Figure 4**) [52].

Activation of  $K_{ATP}$  channels upon damage may play a neuroprotective role by decreasing the cellular metabolic demand, reducing activation rate of the action potential, thus leading to hyperpolarization of the dopaminergic neurons and loss of its normal pacemaker activity [53].

$K_{ATP}$  channels play an important role in signal transduction in the central nervous system (CNS). For example, these channels are implicated in rest potential of most neuronal cell controlling the duration of action potential, firing frequency, and nonspecific intervals, thus regulating pacemaker time [54]. These ionic channels stabilize the membrane potential and the mitochondrial matrix volume during the ATP decline in order to increase the firing in dopaminergic neurons, as well as activation of metabolic pathways to provide cell energy (**Figures 3 and 4**) [25].

During mitochondrial dysfunction caused by oxidative stress or in the presence of neurotoxins (MPTP or rotenone), high calcium concentration and the hyperpolarization of membrane potential may be involved in the reduction of cellular activity in adult rats [52]. However, the vulnerability of dopaminergic neurons may be related to the differential expression of  $K_{ATP}$  (Kir6.2) between STNc and VTA neurons. Acute activation of rotenone-induced  $K_{ATP}$  channels in rat brain slices in responsive dopaminergic neurons increases the expression of the  $K_{ATP}$  channel subunits, the SUR1 and Kir6.2 [55]. However, the chronic effect of ATP depletion and consequent opening of  $K_{ATP}$  channels (Kir6.2/SUR1) due to its metabolic sensitivity in the vulnerable STNc and VTA-DA neurons decrease the expression of the decoupling protein (UCP2) due to the lower degree of mitochondrial decoupling conducted by the metabolic stress in PD [25].

The opening of the  $K_{ATP}$  channels may result in the hyperpolarization of the neurotransmitters modulating the release of glutamate and g-aminobutyric acid (GABA) in the *substantia nigra reticulata* (StNr) and in the striatum, reducing glutamatergic transmission into the brain (**Figure 4**) [56]. This fact suggests the significance of oxidative stress and mitochondrial alterations as a common remarkable cause in the development of PD (**Figures 3 and 4**).

During PD development,  $Ca_v1.2$  in favor of  $Ca_v1.3$  is differentially expressed in brain areas, thus resulting in an increase of neuronal susceptibility to events associated with oxidative stress [1, 24]. The hypothesis of differential expression of  $Ca_v1$  subtypes to explain neuronal selective cell death remains inconclusive, but the fact that there is a change in its prior expression throughout the brain in early stages of the disease's development reinforces our previous proposition that calcium imbalance is a fundamental requirement to understand PD pathogenesis.



### 3. Conclusions

In this review, we suggest that both mitochondrial  $K_{ATP}$  channel and calcium<sub>v</sub>1.3-voltage-gated contribute to maintain a balance between cell proliferation and apoptosis, acting as a metabolic sensor by coupling ROS and glucose metabolism to mitochondrial membrane potential in dopaminergic neurons. Finally, in conclusion, it may lead to a new pathway of drug development and treatment of PD.

#### List of abbreviations

AADC	aromatic amino acid decarboxylase
ABCC8	ATP-binding cassette subfamily C member 8
ADP	adenosine diphosphate
a-syn	alpha-synuclein
ATP	adenosine triphosphate
Cav1.2	voltage-dependent calcium channel subunit alpha 1C
Cav1.3	voltage-dependent calcium channel subunit alpha 1D
CNS	central nervous system
D2-AR	dopaminergic D2-autoreceptor
DA	dopaminergic
DJ1	protein deglycase 1
PD	Parkinson's disease
ETC	electron transport chain
FADH2	Flavin adenine dinucleotide
GABA	g-aminobutyric acid
GPe	external globus pallidus
$K_{ATP}$	potassium channels
KCNJ11	potassium voltage-gated channel subfamily J member 11
Kir6.2	subunit ATP-sensitive $K^+$ channel
L-dopa	L-3,4-dihydroxyphenylalanine
Mito- $K_{ATP}$	mitochondrial ATP-dependent $K^+$ channel
mit-psi	mitochondrial membrane potential
MPP+	metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADH	nicotinamide adenine dinucleotide
NC	nucleus accumbens
ROS	reactive oxygen species
STNc	substantia nigra compacta
STNr	substantia nigra pars reticulata
SUR1	sulfonylurea receptor
TH	tyrosine hydroxylase
UCP2	decoupling protein 2
VMAT-2	vesicular monoaminergic carrier-2
VTA	ventral tegmental area
VTA-DA	ventral tegmental area DA neurons

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