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Potassium channels in the basal ganglia: Promising new targets for the treatment of Parkinson's disease

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Potassium channel diversity and classifications
3.1. Classifications and structure of potassium channels
3.1.1. Voltage-gated K^+ channels
3.1.2. Calcium-activated K^+ channels
3.1.3. Inward rectifier K^+ channels
3.1.4. Two-pore K^+ channels
3.2. Potassium ion channelopathies: dysfunction of potassium channels in the nervous systems
4. Differential distribution of K^+ channels in the basal ganglia
4.1. Potassium channels in the substantia nigra
4.2. Potassium channels in the neostriatum
4.3 Potassium channels in globus pallidus and subthalamus cells
4.4. Potassium channels in mitochondria and glia membranes
5. Roles of potassium channels in the basal ganglia
5.1. Roles of apoptosis-related Kv channels in the basal ganglia
5.2. Roles of fast spiking-related Kv in the basal ganglia
5.3. Roles of K_{ATP} in the basal ganglia
5.4. Roles of Kir2 in the basal ganglia
5.5. Roles of SKCa in the basal ganglia
6. Pharmacological considerations
6.1. Preclinical trial: Roles for K_{ATP} channel openers in PD
6.2. Possibilities for gene therapy targeting at the basal ganglia against PD
7. Perspectives and future directions
8. Acknowledgments
9. References

1. ABSTRACT

A large number of studies indicate that potassium (K^+) channels play important roles in cellular signaling in both excitable and nonexcitable cells. Moreover, a considerable number of K^+ channels within the nervous system appear to mediate diverse cellular signaling, including regulation of neurotransmitter release, neuronal excitability, and cell volume. Recent studies on the K^+ channel gene expression in the basal ganglia reveal dysfunctions of various K^+ channels (e.g., Kv, K_{ATP}, Kir2 and SKCa), which may be involved in the pathogenesis of Parkinson's disease (PD). This review aims to provide an overview of our current understanding of the molecular mechanisms involved in K^+ channel functions in the basal ganglia, and an insight on how to exploit K^+ channels as therapeutic targets in the treatment of PD.

2. INTRODUCTION

Remarkable progress has been made during the past twenty years in understanding the roles of potassium (K^+) channels in the mammalian brain. These critical roles include regulation of neurotransmitter release, neuronal excitability, smooth muscle contraction, and cell volume (1-3). Based on their central positions in metabolic and signaling pathways, K^+ channels are increasingly recognized as potential targets for pharmacological intervention (4-6). For example, the use of sulfonylurea as targeting at the ATP-sensitive K^+ channels (K_{ATP}) in pancreatic beta-cells can lead to increased insulin release in diabetic patients (7-9). These findings have raised the following important question: How can we judge the therapeutic potential of a potential target? Based on previous studies as well as our own research, it appears that

a promising therapeutic target should satisfy the following criteria: 1) there should be tissue-specific localization, and 2) it should mediate biological functions in the structures where it is expressed (10, 11).

Various K^+ channels, such as Kv, K_{ATP}, Kir2 and SKCa, have specific localization and protein expression patterns in the basal ganglia, suggesting that the channels may be, in addition to dopaminergic receptors and dopamine-related transporters, predominant mediators of involuntary movements (12-16). Known dysfunctions of K^+ channels in the basal ganglia have suggested therapeutic potential of K^+ channels for treating PD. In this review, we provide a comprehensive overview of the molecular roles of K^+ channels in the basal ganglia and the potential for developing novel prophylactic or therapeutic approaches targeting distinct types of K^+ channels for the treatment of PD.

3. POTASSIUM CHANNEL DIVERSITY AND CLASSIFICAITIONS

3.1. Classifications and structure of potassium channels

K^+-selective channels belong to the most ubiquitous ion trafficking molecules in living organisms, with at least 100 coding genes in mammals (17). K^+ channels respond to a wide array of stimuli, such as changes in membrane voltage or intracellular levels of certain ions, and small organic molecules and proteins (e.g. Ca^{2+}, ATP, cAMP or G-protein subunits), which may act alone or in combination. Many K^+ channels serve as sensors for cellular metabolic states. In addition, K^+ channels contribute to the maintenance of the resting potential and fine-tuning of excitability in neurons, heart and muscle, mainly by defining action potential duration and the intervals between action potentials.

Traditionally, K^+ currents have been assessed in excitable cells using electrophysiological techniques and classified according to their functions. K^+ channels include the classical delayed rectifier K^+ channels (DRPC, Kr), transient current K^+ channels (KA), inward rectifier K^+ channels (IRPC, Kir), and ligand-gated K^+ channels (LGPC), including Ca^{2+}-dependent K^+ channels and leak currents. Based on their crystalline structure and transmembrane (TM) domains, K^+ channels are subdivided into 2 TM, 4 TM and 6 TM subfamilies. Potassium channels are tetrameric membrane proteins that form TM aqueous pores. Each subfamily of K^+ channel generally consists of a primary pore-forming α subunit that is associated with several regulatory subunits (18-20).

The current classification of K^+ channels is based on molecular biology and gene homology, which was proposed by the International Union of Pharmacology in 2003. This classification is intended to unify and update the different classifications published previously, and divides potassium channels into voltage-gated K^+ channels including classical voltage-gated potassium channels (Kv1.x, Kv2.x, Kv3.x, Kv4.x, Kv5.x, and Kv6.x), KCNQ (KCNQ1, KCNQ2, KCNQ3, KCNQ4 and KCNQ5), HERG; inward rectifier potassium channels (Kir) including classical Kir (Kir1.x, Kir2.x, Kir3.x, Kir4.x, Kir5.x and Kir7.x), ATP-sensitive potassium channels (K_{ATP}), Kir6.x and SUR1/2; Ca^{2+}-activiated potassium channels (KCa) including big conductance (BK), medium conductance (MK) and small conductance (SK) channels and two-pore K^+ channels (K2P; tandem pore) including TREK, TRAAK, TASK, TWIK, TOK, THIK (21-25) .

3.1.1. Voltage-gated K^+ channels

Voltage-gated K^+ channels (Kv1 to Kv12) are widely expressed in excitable cells where they play an essential role in membrane hyperpolarization during an action potential and its propagation along the plasma membrane. Early patch clamp studies on excitable cells including neurons and myocytes revealed the presence of K^+ currents with biophysical and pharmacologic properties typical of Kv channels. More recently, molecular approaches using PCR and selective antibodies directed against Kv α and auxiliary subunits, have demonstrated that excitable cells from various organ systems express a remarkable diversity of Kv channel subunits (23). Classical voltage-gated K^+ channels (Kv) including Kv1-6 are often referred to as shaker-like channels. Kv channels are considered outward rectifiers since they allow current to flow out of the cell instead of into the cell. They are comprised of four individual α subunits and may be associated with one of a number of β subunits. The β subunits are essential for proper channel activity because channels composed of only α subunits do not possess native biophysical activity (23, 26-28). KCNQ channels (Kv7.1-7.5), also known as KCNQ1-5 or neuronal Kv, are mainly expressed in neurons and considered to be delayed rectifiers without fast inactivation (29, 30). KCNQ genes encode a growing family of six TM domains, single pore-loop, and K^+ channel α-subunits that have a wide range of physiological correlates. KCNQ1 (KvLTQ1) is co-assembled with the product of the KCNE1 (minimal K^+-channel protein) gene in the heart to form a cardiac-delayed rectifier-like K^+ current. Mutations in this channel can result in one form of inherited long QT syndrome which is associated with a form of deafness. KCNQ1 can also be co-assembled with KCNE3, which may be the molecular correlate of the cyclic AMP-regulated K^+ current present in colonic crypt cells (31, 32). KCNQ2 and KCNQ3 heteromultimers are thought to underlie the M-current, and mutations in these genes may cause an inherited epilepsy-benign familial neonatal convulsions (BFNC) (33). The KCNQ4 channel is expressed at high levels in the outer hair cells of the cochlea and in a number of nuclei in the brain stem. Mutations in KCNQ4 cause an inherited form of deafness similar with KCNQ1. The recently identified KCNQ5 gene is expressed in the brain and skeletal muscle, and can be co-assembled with KCNQ3, suggesting that it may also play a role in M-current heterogeneity (34, 35). ERG channels (Kv10-12) including EAG, ERG and ELK channels have two unique features: a signature gene sequence in the P loop region that differs from the other channels, and the presence of a cyclic nucleotide binding domain within the cytoplasmic part of the carboxyl terminal. These channels are comprised of six TM segments. All contain a unique and conserved domain

called the 'EAG domain'. The recently identified Herg gene is expressed in cardiac myocytes and neurons, which is crucial for normal action potential repolarization. Blockage of this channel will cause a drug-induced long-QT syndrome (36-38).

3.1.2. Calcium-activated K^+ channels

Ca^{2+}-activiated K^+ channels (KCa) have fewer subfamilies than Kv channels and can be divided into two subfamilies, the small or intermediate conductance K^+ channels (SK/IK), and high conductance K^+ channels (BK, or Maxi-K, Slo). The common characteristic in all KCa channels is that they are activated when the cytoplasmic concentration of Ca^{2+} is increased (Note: however, BK channels are also voltage senstive) (39, 40). SK/IK channels are responsible for the slow after-hyperpolarization following an action potential. These channels are distinguished from BK by their high sensitivity to intracellular calcium, low conductivity and weak voltage dependence. The overall architecture of the SK channel α subunit is very similar to that of the Kv channels: six TM domains (1–6) and a P region, with intracellular N and C terminals. These elements undergo tetramerization to form a functional channel. Moreover, the SK channel possesses a C-terminal Calmodulin-binding domain, which allows the channel to interact with calmodulin and to be regulated by Ca^{2+} (41). BK channels generally provide an inhibitory negative feedback influencing cellular metabolism and excitability. BK channels exist as a tetramer of pore-forming α subunits and a regulatory β subunit. Unlike Kv channels, BK channels have extracellular N-termini owing to an additional transmembrane domain that precedes the six domains homologous to those in Kv channels. The C-terminal is cytosolic and contains a region termed the "calcium bowl", which binds calcium and participates in the activation of the channel, as well as two structures that regulate the conduction of K^+. Although the expression of the α subunit alone is sufficient to generate calcium-dependent K^+ movement, many properties of these channels are affected by co-expression of the β subunits (42).

3.1.3. Inward rectifier K^+ channels

Inward rectifier K^+ channels (Kir1-7) mediate the K^+ transport across the cell membrane and stabilize the resting potential near the K^+ equilibrium potential. Their structure is simpler than Kv and KCa channels and contains only the pore-forming motif of the K^+ channels, i.e., two TM domains and a P region. The N and C termini of these channels are located in the cytoplasm and the functional channel is a tetramer of these pore-forming subunits. These channels function in cooperation with sulfonylurea receptor (SUR) subunits to link cell metabolism to electrical activity and K^+ fluxes (43, 44). This family consists of classical Kir and K_{ATP}. Classical Kir channels (Kir1.x (ROMK1), Kir2.x (IRK1-4), Kir3.x (GIRK1-4), Kir4.x, Kir5.x and Kir7.x) conduct much larger inward currents at membrane voltages negative to the K^+ equilibrium potential than outward currents at voltages positive to it, even when K^+ concentrations on both sides of the membrane are made equal. This conduction property, called inward rectification, is caused by strong voltage dependence and channel blockade by intracellular cations such as Mg^{2+} and polyamines. Functional Kir channels are formed by four pore-containing α subunits that are assembled either of identical subunits or different subunits. The general structure of a Kir channel consists of two membrane-spanning domains with highly conserved pore region (45-47). K_{ATP} are comprised of Kir6.x and SUR1/2 and were found to be expressed in many cell types in various brain regions. K_{ATP} channels are octameric proteins consisting of two different types of subunits: the Kir6 inwardly rectifying K^+ channel subunit and SUR subunits. In functional channels, four pore-forming Kir6 subunits are joined together with four regulatory SUR subunits. At present, two members of the Kir6 family (Kir6.1 and Kir6.2) have been cloned, and two SUR isoforms (SUR1 and SUR2) have been identified. A variety of SUR1 and SUR2 splice variants have been described, with much focus being placed on SUR2A and SUR2B because they give rise to functional K_{ATP} channels with different biophysical, pharmacological, and metabolic properties. Kir6.2 in combination with SUR1 subunits form K_{ATP} channels with properties very similar to those described in pancreatic beta cells. Kir6.2 and SUR2A pairs resemble the K_{ATP} channels found in cardiac and skeletal muscle, and SUR2B in combination with Kir6.1 subunits generate K_{ATP} channels that possess properties reminiscent of those studied in smooth muscle (48-50).

3.1.4. Two-pore K^+ channels

Two-pore K^+ channels (K2P; tandem pore) are thought to underlie many leak currents in native cells and play integral roles in cell signaling pathways by modifying cell membrane resting potential. At present 14 members of this family have been discovered, including TREK, TRAAK, TASK, TWIK, TOK and THIK. Inclined to open under the adjustment of multiple voltage potential, these channels are diffusely modulated by multitudinous neurotransmitters and other biochemistry factors. The α subunits that constitute the K2P channel contain two pore-forming motifs linked in tandem, which is constituted by four TM domains and two P regions. Generally, the dimers of α subunits are viewed as compositions of functional K2P channels. Although the function and pathology of these channels are not well understood, it is widely recognized that chemical mediators, mechanical cellular changes, and physiologic diversification of the intracellular and extracellular circumstances contribute to the modulation of K2P channels (51).

3.2. Potassium ion channelopathies: dysfunction of potassium channels in the nervous system

Currently more than ten ion channel coding genes have been identified as causative factors of human hereditary diseases and acquired disorders with malfunction of ion channels. Mutations in genes encoding channel proteins or the presence of autoantibodies to ion channels are increasingly being implicated in the pathology of various diseases. This kind of disorder is termed 'channelopathies' (52-55). Thus, dysfunctions of K^+ channels due to mutations of K^+ channel protein genes or the presence of auto-antibodies to K^+ channels ion are called 'potassium channelopathies' (56, 57). With the

development of molecular techniques such as the positional cloning method, the number of identified channelopathies is growing rapidly. The first discovery that mutations in a K^+ channel gene can cause an inherited disease was reported in 1994 (58). Because of the great diversity of K^+ channel genes and the importance of these channels in various organs, K^+ channelopathies are one of the most common and ubiquitous ion channel disorders, with the exception of cardiac K^+ channelopathies. Most K+ channelopathies have been found in the nervous system and the neuromuscular junction, e.g., epilepsy, spinocerebellar ataxia and neuromyotonia (58-60). There is mounting evidence suggesting the involvement of ion channels in the progression and pathology of many neurological disorders. The focus of this review is on one of the most prevalent neurodegenerative diseases in the world-PD. Further understanding of K^+ channelopathies and the functions of K^+ channels in the basal ganglia may be critical in developing new therapies for PD.

4. DIFFERENTIAL DISTRIBUTION OF K^+ CHANNELS IN THE BASAL GANGLIA

Structures in the basal ganglia are integral in controlling involuntary movement and cognitive functions. In the basal ganglia circuit, cortical inputs reach separate subpopulations of striatal γ-aminobutyric acid (GABA)-containing medium-sized spiny neurons. From the striatum, cortical information is transmitted to the substantia nigra (SN) pars reticulata through parallel routes called the 'direct' and 'indirect' pathways. Information is also transmitted to other output structures of the basal ganglia (i.e., globus pallidus, subthalamic nucleus and thalamus) and then sent back to the frontal cortex. This circuit plays a key role in the regulation of voluntary and purposeful movements as well as in behavioral control and cognitive functions. Selective neuronal loss in any part of the circuit results in clinical syndromes characterized by motor and cognitive dysfunctions such as those found in PD. The key pathological feature of PD is heterogenous loss of pigmented dopaminergic neurons in the SN pars compacta and their afferent projections to the striatum (61, 62).

There are various distributions of potassium channels in neurons versus glia, and even plasma membranes versus mitochondria, in the basal ganglia. The potassium channels distributed in the basal ganglia not only take part in the discharge of the circuit, but are also involved in the release of neurotransmitters, apoptosis and hypoxia. Thus the distribution of potassium channels in specific structures or cells may influence the functions of those structures and cells.

4.1. Potassium channels in the substantia nigra

The SN is divided into the pars compacta and the pars reticulata. The pars compacta contains dopamine neurons corresponding to approximately 3–5% of total neurons in the SN. These dopamine neurons send their axons along the nigrostriatal pathway to the striatum where they release dopamine. Degeneration of cells in this region is the principal pathology that underlies PD, a disease which constitutes a major public health burden in developed countries and even some developing countries such as China (63) where the average life expectancy is over 71 years. By contrast, neurons in the pars reticulata are much less densely packed than those in the pars compacta. Most of these neurons produce GABA, but there is also a small sub-population of dopamine neurons. The GABA neurons connect to portions of the thalamus and brainstem, and also make connections to the dopamine neurons in the pars compacta. The pars reticulata is considered to be one of the two primary output nuclei of the basal ganglia; and the other output is the internal segment of the globus pallidus, which is largely involved in the orientation and control of eye movements. In addition to neurons, there are astrocytes that are involved in immune-inflammation reactions.

It is thought that Kv channels are expressed in all cells in the SN and take part in the mechanism underlying apoptosis, hypoxia and intrinsic pacemakers. Previous reports have localized various Kv channel mRNAs and proteins in the SN and several comprehensive studies have described varying Kv channel expression patterns. Chung et al. found prominent expression of Kv1.4 in the pars reticulata and Kv1.2 in the pars compacta (16). Serodio et al. found that the pars compacta expressed mainly Kv4.3 proteins that are thought to form fast inactivating K^+ channels. These channels activate and inactivate at subthreshold potentials and recover from inactivation at a faster rate than other inactivating Kv channels (64). In another study, Kv4.3 and KChip3 subunits were found to mediate an A-type potassium channel that was tightly associated with the pacemaker frequency of individual dopaminergic SN neurons (65).

The Kir6 family (Kir6.1 or Kir6.2) and sulfonylurea receptors (SUR1 or SUR2) are also expressed in SN. Previous studies in the rat SN have shown that the Kir6.1 subunit is predominantly expressed in astrocytes whereas the Kir6.2 subunit is exclusively expressed in neurons (66). In addition to the astrocytic expression, the Kir6.1 protein is also found in a small populations of neurons in distinct areas of the brain, such as the hypothalamic supraoptic and paraventricular nuclei and the striatum (10). Compared to Kir6.1, Kir6.2 is prominently expressed in high density in dopaminergic neurons (67, 68).

4.2. Potassium channels in the neostriatum

The neostriatum is involved in the induction of purposeful movements and in the suppression of other movements. It acts through the internal segment of the globus pallidus and the SN, which receives input from striatal spiny neurons. The striatum can be divided into patch and matrix compartments based on neurochemical markers and connectivity. Input from the matrix is predominantly related to sensorimotor processing, whereas patch input has a strong relation to the limbic system (69). Traditional classifications of neurons in the neostriatum consist of aspiny neurons and spiny neurons according to the morphological characteristics. Aspiny interneurons in the striatum receive various excitatory inputs, which determines whether spiny projection neurons fire or not

(70, 71). Both spiny and aspiny striatal cells have been shown to be heterogeneous in their physiological, chemical and connectivity characteristics. Over 90% of the striatum is comprised of medium-sized spiny (MS) projection neurons and they are the major targets of extrinsic afferents. The remaining neurons are comprised of four types of interneurons: 1) fast-spiking (FS) GABAergic neurons, 2) cholinergic large aspiny cells, 3) NOS–NADPH-positive interneurons, and 4) calretinin-positive interneurons. Among these neurons, MS, FS and large cholinergic interneurons play more crucial roles than the other cell types in modulating striatal outputs. MS neurons play an important role in integration of synchronous inputs from many cortical cells and regulation of the direct and indirect pathways. FS interneurons receive direct inputs from the cerebral cortex and synapse on MS neurons. Although the neurons constitute less than 1% of the cells in the dorsal striatum, FS interneurons play a crucial role in shaping striatal output by mediating cortical feed-forward inhibition of MS neurons (72). Large cholinergic striatal interneurons account for only 1–2 % of the total neuronal population, while supplying this area with one of the highest concentrations of acetylcholine in the whole brain. Similar to dopaminergic inputs, cholinergic interneurons also exert opposite regulatory effects on the two distinct populations of striatal efferent GABAergic neurons in the direct (movement facilitating) and indirect (movement inhibiting) basal ganglia pathways. In contrast to the dopaminergic system, however, which activates the direct pathway via D1-receptors and depresses the indirect pathway via D2-receptors, the large cholinergic interneurons suppress movement by inhibiting direct pathway output neurons via M4-receptors and furthermore by activating the indirect pathway output neurons via M1-receptors (11).

The Kv3 subfamily (Kv3.1–Kv3.4) displays prominent expression in the striatum, influencing the ability of cells to accelerate the repolarization of the action potential efficiently and specifically. In the striatum, the Kv3.1, Kv3.2 and Kv3.4a proteins are expressed prominently in FS cells and in fact are a significant determinant of the fast-spiking discharge pattern. Kv3.4a can also modify the gating of Kv3.1b channels (73, 74). In addition to somatic expression, Kv3.1 and Kv3.2 proteins also are prominently expressed at FS cell terminals, suggesting roles for Kv3 channels in neurotransmitter release (75).

Kir6 channels (Kir6.1 or Kir6.2) and SUR (SUR1 or SUR2) are also expressed in the striatum. In addition to its astrocytic expression, Kir6.1 protein is also found in large cholinergic interneurons, while Kir6.2 is exclusively expressed in neurons in the striatum (11). Moreover, Kir2 family proteins are detected on somata and dendrites of most striatal neurons. However, the Kir2.3 protein is preferentially expressed in striatal matrix areas, and the Kir2.4 subunit is most prominently displayed by the tonically active, large cholinergic interneurons of the striatum. These two Kir2 subunits are among the key players in regulating dopaminergic and cholinergic neurotransmission within the striatum, and therefore are of major importance for the output of the basal ganglia (12, 14, 76).

4.3. Potassium channels in globus pallidus and subthalamus cells

Advances in the recent anatomical and electrophysiological studies suggest that globus pallidus (GP), which have traditionally been viewed as relay in the 'indirect pathway', is interconnected with all major basal ganglia nuclei. There is evidence suggesting that the axons of GP neurons form large, perisomatic baskets around target neurons, almost the same as those in cortex, hippocampus, and cerebellum. However, unlike the interneurons that extend only near to local neurons, the axon of a single GP neuron can elongate faraway innervating variety of neuronal types neurochemically and functionally. The available extension of connectivity of GP neuron, combined with the perisomatic targeting of their synapses, suggest its pivotal role in global basal ganglia function. Morphological and electrophysiological studies performed in rodents and primates have found that the predominant cell type in the GP express GAD67 and parvalbumin. The cells have arborizing dendrites and axons that project to the subthalamic nucleus (STN). This population of GP neurons is intermixed with ENK-expressing GABAergic neurons that predominantly project back to the striatum. The observed heterogeneity of cellular makeup within the confine of the GP is due in part to a displaced population of basal forebrain cholinergic neurons near the medioventral portion of the GP. There is some evidence that the properties of GP neurons are overlapping and highly depend on threshold and sensitivity of the assays. The principal excitatory input to the GP arises from the STN, but it accounts for less than 10% of synapses impinging onto GP neurons (77). In contrast, the STN has been regarded as an important modulator of basal ganglia output: It receives its major afferents from the cerebral cortex, thalamus, globus pallidus externals and brainstem, and projects mainly to both segments of the GP, SN, striatum and brainstem. The STN is essentially composed of glutamatergic projection neurons. Under resting conditions, the tonic activity of the STN drives, in part, the tonic activity of its target nuclei. STN plays a pivotal role in normal process of movement through high-frequency electrical activity in response of the basal ganglia to cortical and thalamic activation. While in PD, the deviant, rhythmic eruption of discharge activity of STN is an essential mechanism in the pathology of the disease. Therefore, treatment such as high-frequency electrical stimulation seems to be helpful in ameliorating some motor symptoms (78).

Several kinds of Kv channels are expressed ubiquitously in the GP. Studies using immunohistochemistry and/or mRNA detection have found that Kv1.4 and KCNQ2 subunits have strikingly high levels of expression in the GP and that these channels all contribute to the increased seizure susceptibility in humans (16, 79). GABAergic projecting PV-containing pallidal neurons co-express Kv3.1 and Kv3.2 K^+ channel proteins and both Kv3.1 and Kv3.2 antibodies co-precipitate channel proteins from pallidal membrane extracts

solubilized with nondenaturing detergents. This specific expression of Kv3.1-Kv3.2 may play a role in helping maintain sustained high-frequency repetitive firing as they probably do in other neurons (80). In most GP neurons A-type currents have been observed, consistent with the presence of the Kv4.2 subunit and several modifying proteins such as KchIPs. There are a variety of excitable cells in the GP that have a high density of K_{ATP} (81). In addition, GIRK4 (Kir3.x) mRNA was found to be restricted to some neuronal populations, such as neurons of the GP and the ventral pallidum. GIRK channels mediate the synaptic actions of numerous neurotransmitters in the mammalian brain and were recently shown to be candidates for genetic mutations that can cause neuronal death (82).

There are two specific K^+ channels expressed in STN neurons. One is SK (2.1-2.3), which contributes to afterhyperpolarizations (AHPs) to control neuronal excitability. These channels are activated by Ca^{2+} binding to calmodulin. This induces conformational changes resulting in channel opening. Channel deactivation is the reverse process produced by dissociation of Ca^{2+} from calmodulin. Hallworth et al. found that in rat STN, apamin-sensitive SK channels are critical determinants of the precision, pace, and pattern of AP generation through their selective coupling to Cav channels (83, 84). The other K^+ channel expressed in STN neurons is Kv3.1 α, which consists of persistent, outwardly rectifying, Cs^+-permeable, K^+ currents. These channels are not necessary for ordinary pacemaking but might be important for sustained, high frequency pacemaking in the STN (85).

4.4. Potassium channels in mitochondria and glia membranes

Mitochondria play a fundamental role in energy generation within cells of the basal ganglia. Apart from this canonical role, mitochondria are involved in other complex processes such as apoptosis. Mitochondrial membrane permeabilization induces the release of cytochrome c, Smac/DIABLO, and AIF, which activates various apoptosis pathways. Recently, an essential mode of K^+ transport through mitochondrial innermembrane was identified to produce cytoprotection. This transport is strictly ion channel dependent, and accordingly, resembles plasma membrane ion channel activity. Potassium-selective ion channels were found to be present in inner mitochondrial membranes. Potassium ions control mitochondrial metabolism primarily due to the regulation of matrix volume. There are many kinds of mitochondrial K^+ channels including ATP-regulated K^+ ($mitoK_{ATP}$) channels, large conductance Ca^{2+}-activated K^+ (mitoBKCa) channels and voltage-dependent K^+ (mitoKv1.3) channels which were found to resemble some of the K^+ channels present in the plasma membrane of various cell types and contribute to the K^+ permeability of mitochondria (86, 87).

In addition to neurons, various K^+ channels (e.g., Kv channels) are expressed in the glia in the basal ganglia (88). However, these cells appear to play different roles than the glia in other parts of the brain that tend to help maintain K^+ ion concentrations at a constant level. Recently, Hu et al. found that $mitoK_{ATP}$ may mediate the effects on rotenone-induced morphological alterations, decrease tumor necrosis factor α (TNF-α) production and decrease expression and activity of an inducible isoform of nitric oxide synthase (iNOS) in a microglial cell line (89). More studies are needed to fully understand the distinct role of K^+ channels in glia in the basal ganglia.

5. ROLES OF POTASSIUM CHANNELS IN THE BASAL GANGLIA

The widespread distribution of the K^+ channels in the basal ganglia suggests that they may influence cellular functions in this part of the brain, e.g., regulating neurotransmitter release, neuronal excitability, smooth muscle contraction, and cell volume. Thus if the functions mediated by K^+ channels are compromised or altered, there may be significant pathological changes in brain.

5.1. Roles of apoptosis-related Kv channels in the basal ganglia

In recent years studies have focused on the involvement of K^+ channels in the apoptosis of most mammalian cells and their central role in metabolic and signaling processes. Recent evidence has strongly suggested that K^+-channel-mediated signals (especially Kv channels) play important roles in the regulation of apoptosis. Apoptotic cell shrinkage, an early hallmark of apoptosis, is regulated by K^+ efflux and K^+ channel activity. Opening of sarcolemmal K^+ channels increases efflux or loss of cytoplasmic K^+ and induces apoptotic volume decrease. In contrast, closure or downregulation of K^+ channels decelerates apoptotic cell shrinkage and attenuates apoptosis. In addition to its role in the control of cell volume, maintenance of a high cytosolic K^+ concentration is required for suppression of caspases and endonucleases, the final mediators of apoptosis. Therefore, enhanced K^+ efflux is an essential mediator not only of early apoptotic cell shrinkage but also of downstream caspase activation and DNA fragmentation. Among the several types of Kv channels, the outward delayed rectifier (IK) channels are believed to play important roles in apoptosis, due to their high K^+ conductance and their non- or slow-inactivation behavior during membrane depolarization. In fact other types of K^+ channels, such as IA and Task leak K^+ channels, may mediate pro-apoptotic K^+ efflux in some cases (90-92).

Dopaminergic neurons in the SN express various Kv channels, such as IA, Kv4.3, IK and Kv1.2, which act as permissive cell death signals. McLaughlin et al. found that K^+ efflux accompanying oxidant-induced apoptosis is mediated by an enhancement of voltage-gated K^+ currents triggered by the oxidative liberation of intraneuronal Zn^{2+}. This change in K^+ currents leads to a p38-mediated exocytotic insertion of Kv2.1-encoded channels (93). Pal et al. found that voltage-gated channels like Kv2.1 are directly linked to oxidative signaling processes (94). Oxidative stress is commonly and intimately associated with nigral cell death in PD literature. Therefore, Kv2.1 channels play a crucial role in the process of oxidative stress-associated cell death in SN. Recently, Kv2.1 channels have been shown to be a major binding partner of dopamine transporter (DAT).

Redman et al. found that Kv2.1 channels mediate the actions of 6-hydroxydopamine (6-OHDA) toxicity --- a condition associated with PD. Moreover, ScTX, a selective Kv2.1 blocker, has neuroprotective actions suggesting that this channel mediates K^+ efflux in dopaminergic neurons undergoing apoptosis. It has been shown that 6-OHDA increases Kv currents in cultured midbrain dopamine neurons and this toxicity was blocked with Kv channel antagonists. 6-OHDA triggers the oxidant-associated Kv channel-dependent cell death pathway that is conserved in non-dopaminergic cortical neurons and midbrain dopamine neurons (95). Taken together, these studies suggest that Kv channels may provide novel therapeutic targets for neuroprotection in PD and related disorders.

5.2. Roles of fast spiking-related Kv in the basal ganglia

Autonomous pacemakers in neurons with periodic spiking in the absence of synaptic input are important participants in a wide array of neural circuits including the basal ganglia circuit, which is rife with fast and slow pacemakers. The pacemakers in the basal ganglia can be divided into two categories based on rate of pacemaking and intrinsic properties. The first category is principal neurons in the GP, STN and SN, which are nominally fast-spiking pacemakers, capable of sustaining discharge rates in excess of 200 Hz for sustained periods. The second category is striatal cholinergic interneurons and dopaminergic neurons, which are slowspiking pacemakers, typically spiking at low frequencies (0.2–10 Hz). These channels are not necessary for ordinary pacemaking but might be important for sustained, high frequency pacemaking (96). It is widely accepted that K^+ channels with Kv3.1 or Kv3.2 subunits underlie fast, delayed-rectifier (DR) currents that endow neurons with this FS ability. The co-expression of Kv3 channels and Na^+ channels creates a potent biophysical mechanism for high frequency discharge. In the GP and STN, the Kv3.1 and Kv3.2 proteins are expressed prominently in a subset of GABAergic interneurons known as FS cells and are a significant determinant of the fast-spiking discharge pattern (80).

Based on the involvement of Kv3 proteins in FS characteristics, Baranauskas et al. coassembled a splice variant of Kv3.4 with Kv3.1 subunits in rat brain FS neurons and found that spike repolarization was more efficient in these channels and that spike duration was reduced, thus enabling higher repetitive spike rates (70). These results suggest that alterations in subunit composition could alter the functional properties of neurons in diseased states. For example, in PD, the FS neurons in the GP and STN often discharge in rhythmic, high frequency bursts. This pattern of discharge is thought to be a critical determinant in the pathophysiological consequences of PD motor symptoms and serves as a rationale for deep-brain stimulation and lesion. The suppression of Kv3.4a expression in STN neurons could prove to be an effective therapeutic alternative in that it should selectively eliminate high-frequency bursts without otherwise disrupting neuronal function.

5.3. Roles of K_{ATP} in the basal ganglia

K_{ATP} channels are activated by decreased ATP/ADP ratios, which belong to a class of inwardly rectifying K^+ channels. Through these channels decreased ATP/ADP ratios produce hyperpolarization leading to decreased cell activity and energy consumption, thus linking metabolic state to excitability. While the channels are widely expressed in the brain, K_{ATP} channels are expressed at high levels in nigrostriatal dopamine cells. It is noteworthy that K_{ATP} channels in many brain cell types are normally closed. For example, in dopamine neurons in the SN pars compacta, K_{ATP} channels do not contribute to resting membrane properties. Consistent with these properties of the channels, activation of K_{ATP} channels by specific openers or by metabolic inhibition can lead to decreased release of several neurotransmitters, resulting in reduced energy consumption during metabolic stress such as hypoxia. These studies suggest that brain K_{ATP} channels may produce neuroprotective effects during metabolic stress (97-100). In addition to plasma K_{ATP} channels, there are many K_{ATP} channels in the mitochondria of cells in the basal ganglia. MitoK_{ATP} channels modulate inner membrane potential and oxyradical production. Mitochondrial K^+ fluxes can affect cytochrome c release and caspase activation and may determine whether neurons live or die in experimental models of stroke and Alzheimer's disease. Therefore, both the K_{ATP} on plasma membranes and mitochondria K_{ATP} play neuroprotective roles in the basal ganglia. Activation of mitoK_{ATP} protects the brain against injury, and this is probably mediated by attenuating mitochondrial Ca^{2+} overload and thus inhibiting mitochondrial permeability transition pore opening during brain ischemia and reperfusion (16, 80).

Recently, Liss et al. provided new evidence that K_{ATP} channels may help determine the selective loss of SN, but not ventral tegmental, dopamine cells in PD. They reported that the mRNA encoding K_{ATP} channels comprising Kir6.2 and SUR1 are abundantly expressed in SN dopamine neurons. They found that metabolic challenges with parkinsonism-inducing toxins, such as 1-methyl-4-phenyl-1,2,3,6-tertrahydropyridine (MPTP), cause rapid hyperpolarization and electrical 'silencing' of dopamine cells in the SN, but not in the ventral tegmental area. In contrast, nigral dopamine neurons from Kir6.2 knockout mice were not hyperpolarized with these toxins. These studies suggest that the K_{ATP} channel may help determine whether a dopamine neuron lives or dies. Additionally, several studies revealed that systemic administration of K_{ATP} openers, such as iptakalim, had neuroprotective actions on acute or subacute PD animal models. However, it is still unclear exactly how K_{ATP} channel–mediated silencing of dopamine neurons triggers cell death. K_{ATP}-induced silencing of dopamine neuron activity ultimately works through a series of interconnected brain regions, which may also underlie the therapeutic effects of deep brain stimulation in PD. Alternatively, decreased membrane excitability and firing rates of dopamine neurons may disrupt autaptic trophic support (self-produced growth factors). Therefore, neuronal silence mediated by K_{ATP} may not always be the key (67, 101). Further studies about K_{ATP} openers and neuroprotection against pathological

states such as PD are needed in both acute and chronic models of disease.

There is an interesting phenomenon that in different structures of the basal ganglia, modulations of K_{ATP} have different pharmacological effects. Spontaneous, as well as amphetamine-induced, locomotor activity are attenuated by administration of glipizide (a sulfonylurea) into the dorsal pallidum and spontaneous locomotor activity is enhanced by (−)-cromakalim, a potassium channel opener (102). Intrapallidal administration of diazoxide, another K_{ATP} channel opener ($K_{ATP}CO$), reduces akinesia in rats with reserpine-induced parkinsonism (103). Lamensdorf *et al*. reported that administration of Kir6.2 antisense ODN significantly attenuated apomorphine-induced contralateral turning and specifically reduced Kir6.2 mRNA in the injected GP in 6-OHDA induced PD models. This demonstrated that reduction in the expression of Kir6.2 in GP projections to the SNr and other nuclei presumably increases GABA release from presynaptic sites. Subsequently, enhanced GABA transmission in these nuclei attenuates apomorphine-induced contralateral turning in 6-OHDA treated rats (104). However, because of the variety of neurotransmitters (dopamine, GABA and glutamate) in the different structures of the basal ganglia, it is difficult to predict the actions of any modulators.

5.4. Roles of Kir2 in the basal ganglia

Kir channels modulate cellular excitability, membrane potential, and secretion of neurotransmitters and hormones. In the Kir channel family, the Kir2 family (Kir2.1, Kir2.2, Kir2.3, and Kir2.4) has the strongest inward rectification. Interestingly, Kir2 channel expression is detected only in neurons but not in glial cells. All Kir2 channels, especially Kir2.3 and Kir2.4 subunits, are present in striatal neurons. Pruss et al. found that the distribution of these two channels was not homogeneous. Striatal patch areas were largely devoid of the Kir2.3 protein, and the Kir2.4 subunit was most prominently expressed on tonically active, giant cholinergic interneurons. The heterogeneous localization of the Kir2.3 and Kir2.4 subunits with respect to these strategic structures suggests these channel proteins to be promising targets for future pharmacological efforts. While studying MSN, Ariano et al. reported that there are decreases in the expression of the K+ channel subunit proteins, Kir2.1, Kir2.3, and Kv2.1, which contribute to the formation of the channel ionophores for these currents. Attenuation in K+ conductances and channel subunit expression contribute to altered electrophysiological properties of MSNs and may partially account for selective cellular vulnerability in the striatum (105, 106). While there are no other reports similar to this, we have seen a similar phenomenon in PD models (unpublished data). Future studies are necessary to further examine this role for K+ channels.

5.5. Roles of SKCa in the basal ganglia

SK channels form a signaling complex with calmodulin as a calcium sensor, the opening of which depends solely on changes of the intracellular calcium concentrations. In neurons, this occurs during and after an action potential. Activation of SK channels hyperpolarizes the membrane, thus reducing cell excitability for several tens or hundreds of milliseconds. This phenomenon is called afterhyperpolarization (AHP), which control neuronal excitability. In the mammalian brain, the three SK channel subunits (SK1-3) display partially overlapping distributions. However, only the SK3 subunit has high levels of gene expression in the basal ganglia while the SK1 and SK2 subunits have high levels of gene expression in the neocortex and hippocampus. At the cellular level, SK1- and SK2-like immunoreactivity has been primarily localized to somatic and dendritic structures, whereas the majority of SK3-like immunoreactivity is associated with varicose fibers. SK channels may play a role in physiological and pathological conditions and have been shown to be involved in the control of memory and cognition (13, 107).

It has been shown that SK3 subunits control pacemaker frequency and precision in dopamine neurons of the SN, and previous studies have implicated SK channels in the transition from burst firing. Wolfart et al. found that the coupling of SK to T-type channels provided stability for spontaneous pacemaker activity, and, in some dopaminergic SN neurons, T-type channel inhibition is sufficient to induce intrinsic burst firing. This has important functional implications for the temporal integration of synaptic input and might help to explain how dopamine neurons switch between pacemaker and burst-firing modes in vivo (108, 109). Another region with high levels of SK3 gene expression is the STN. Nicholas et al. found that SKCa/Cav2.2 channel coupling did not underlie spike-frequency adaptation but limited activity in response to current injection by encoding the accumulation of intracellular calcium, maintained the characteristic sigmoidal frequency-intensity relationship and generated a post-train AHP. SKCa channels play a fundamental role in autonomous, driven, and rebound activity and oppose the transition from autonomous, rhythmic, single-spike activity to burst firing in STN neurons (80).

6. PHARMACOLOGICAL CONSIDERATIONS

Suitable candidates for pharmacological targets should fulfill at least two criteria. First, it should have tissue-specific localization and second, it should mediate biological functions in the structures in which it is expressed. Various K^+ channels (e.g., Kv, K_{ATP}, Kir2 and SKCa) have specific localization in the tissue, as well as widespread distribution of channel proteins in the basal ganglia. Taken together, this suggests that K^+ channels may be a predominant mediator of involuntary movements (in addition to dopaminergic receptors and dopamine-related transporters). Pharmacological therapies can take advantage of the diversity of K^+ channels (as shown by molecular biological techniques) and the intense medicinal chemistry efforts that have focused on the synthesis and development of modulators of various K^+ channels, including Kv, SK and K_{ATP}. Additionally, gene therapies can employ new technologies focusing at delivery and

Table1. K_{ATP}COs and PD models *in vivo and in vitro*

Compound	Injury Model	Observed Protective Effect	Mode of Treatment	References
Iptakalim (Ipt), a novel K_{ATP}CO	Unilateral 6-OHDA lesioned rats□primary cultured rat astrocytes	Increase extracellular dopamine levels in the lesioned side of the striatum and decrease dopamine levels in the intact side of the striatum. And decrease glutamate levels in the lesioned side of the striatum of PD rats.	Ipt (0.75, 1.5, 3.0 mg/kg/day, p.o.) were administered for 21 days.	Effects of systemic administration of iptakalim on extracellular neurotransmitter levels in the striatum of unilateral 6-hydroxydopamine-lesioned rats.
Iptakalim	Rotenone-treated rats	Improved behavioural dysfunction □elevated dopamine contents □reduce enzymic activities and mRNA levels of inducible nitric oxide synthase (iNOS).	Ipt (0.75, 1.5, 3.0 mg/kg.d p.o.) for 14 days.	Activation of mitochondrial ATP-sensitive potassium channels improves rotenone-related motor and neurochemical alterations in rats.
Iptakalim	6-OHDA and haloperidol rat models	Reverses haloperidol-induced parkinsonism.	Intraperitoneal injection of Ipt (0.125 mg/kg, 0.25 mg/kg or 0.5 mg/kg) for sixty minutes before injection of haloperidol.	Studies of ATP-sensitive potassium channels on 6-hydroxydopamine and haloperidol rat models of Parkinson's disease: implications for treating Parkinson's disease?
Iptakalim	Rotenone-induced male Sprague-Dawley rats	Prevent rotenone-induced behavioral alterations and DA, NE, and 5-HT deletion in the nigrostriatal system of rats. And reduced the activity of iNOS.	Ipt (1.5 mg/kg/day, orally) for 3 days.	Systematic administration of iptakalim, an ATP-sensitive potassium channel opener, prevents rotenone-induced motor and neurochemical alterations in rats.
Iptakalim and pinacidil ,an non-selective K_{ATP}CO	Rotenone-induced PC12 cells	Alleviate the cytotoxicity of rotenone , and decrease the extracellular DA levels elevated by rotenone.	Pretreatment with 10 μM Ipt , and treatment with 1, 10 and 100 μM Ipt for 15 min before treated with rotenone.	Effects of iptakalim on rotenone-induced cytotoxicity and dopamine release from PC12 cells.
Iptakalim	MPP^+ on SH-SY5Y cell	Modulate glutamate transporters and subsequently alleviate the increase of extracellular glutamate levels induced by MPP^+ through opening mitoK_{ATP} channels.	Treatment with Ipt (0.01–100 μM), and pre-incubation with Ipt 0.1 μM for 20 min before MPP^+.	ATP-sensitive potassium channel opener iptakalim protected against the cytotoxicity of MPP^+ on SH-SY5Y cells by decreasing extracellular glutamate level.
Iptakalim		Restored DA neuronal firing during rotenone-induced hyperpolarization and suppressed rotenone-induced outward current.	300 mM Ipt perfusion.	Iptakalim modulates ATP-sensitive K^+ channels in dopamine neurons from rat substantia nigra pars compacta.
Pinacidil	Rotenone-Induced PC12 Cell	Cell viability was significantly increased by preconditioning with pinacidil.	PC12 cells were exposed to pinacidil for 15 min.	Activation of adenosine triphosphate-sensitive potassium channels confers protection against rotenone-induced cell death: therapeutic implications for Parkinson's disease.
Diazoxide, selective mitochondrial K_{ATP}CO	Rotenone-induced male Sprague-Dawley rats	Improved behavioural dysfunction □elevated dopamine contents □reduce enzymic activities and mRNA levels of iNOS.	Treatment with L-dopa (10 mg/kg.d p.o.) , Ipt (0.75, 1.5, 3.0 mg/kg.d p.o.) and diazoxide (3.0 mg/kg.d p.o.) for 14 days.	Activation of mitochondrial ATP-sensitive potassium channels improves rotenone-related motor and neurochemical alterations in rats.

selective targeting of channel proteins by gene interference via antisense oligonucleotides or siRNA.

6.1. Preclinical trials: Roles for K_{ATP} channel openers in PD

In recent years, K^+ channels in general and K_{ATP} channels in particular have attracted increasing interest as targets for drug development, and the modulators of K^+ channels , especially, the K_{ATP}COs were seen as one of most potential agents. Up to now, there are at least three generations of K_{ATP}COs developed with medicinal chemistry efforts on K_{ATP} channels. The first generation K_{ATP}COs, such as cromakalim, pinacidil, and nicorandil, were primarily applied for the treatment of hypertension. Second generation K_{ATP}COs, which differ from the first generations by a significantly improved selectivity, have broadened chemical diversity of K_{ATP} channel ligands including the cyclobutenediones and dihydropyridine related structures. These new K_{ATP}COs offer an entirely new chemotype within the K_{ATP}CO field --- the tertiary carbinols. Among the second generations, there are certain drugs that have important actions to modulate th secretions of vital hormone *in vivo* or *in vitro*. For example, as an K_{ATP}CO that open Kir6.2/SUR1 channels, diazoxide have clinical application for treatment of hypersecretion of insulin associated with certain tumours (insulinoma) and genetic disorders (persistent hyperinsulinemia and hypoglycemia of infancy). However, the clinical use of diazoxide has been hampered by its lack of potency and selectivity, giving rise to side effects, such as edema and hirsutism. Thus, new selective openers of Kir6.2/SUR1 channels have been pursued. To avoid these problems, the third generation of K_{ATP}COs with higher selectivity, similar to 1,2,4-thiadiazine 1,1-dioxide derivatives (e.g., BPDZ 62, BPDZ 73, NNC 55-0462, NNC 55-0118 and NN414, cyanoguanidines, nitropyrazoles and 4-sulfamoylphenylbenzamides), have been developed. NN414 has been shown to be a potent and selective opener for Kir6.2/SUR1 K_{ATP} channels, which inhibit glucose-stimulated insulin release and has shown beneficial effects on glucose homeostasis in preclinical and clinical studies (7, 110-114). Recently, there have been a series of studies focusing at treatment of PD using K_{ATP}COs *in vivo* or *in vitro (*Table 1) (115-122). The K_{ATP}COs used are mainly iptakalim, diazoxide and pinacidil which belong to both the

first and the second generation of K_{ATP}COs. Because the majority of these studies have been conducted using animal or cellular models, future studies should focus on clinical applications of the drugs in humans.

In addition to K_{ATP}COs, there are other K^+ channel modulators that have been developed quickly in recent years, including blockers of SK and Kv channels. However, there have been only a few reports regarding the use of these blockers on PD (95, 123, 124).

6.2. Possibilities for gene therapy in the basal ganglia against PD

Many groups have sought gene therapy for PD, but so far the genes of K^+ channels have not been the target genes for PD. Lee et al. found that increased expression of SK2 or Kv1.1 via viral vectors not only protected against kainate or glutamate excitotoxicity, but also increased cell survival after treatment of sodium cyanide or staurosporine in cultured hippocampal neurons (125). They also found that animals overexpressing SK2, but not Kv1.1, exhibited a post-training memory deficit. This difference raises the possibility that alterations of K^+ channel subtypes can both harm and enhance brain functions. This study also raises the possibility that gene therapy targeting at K^+ channels may produce therapeutic effects against PD.

Among the K^+ channels that are expressed and distributed in the basal ganglia, there are several types with marked tissue-specificity making it possible to target K^+ channels for treatment. There are some reports about K^+ gene therapy altering excitability or changing the viability of target cells or tissues in cardiac diseases and erectile dysfunctions (126-130). We propose two possible directions for the gene therapy targeting at K^+ channels: One is to modulate cell viability and improve survival through knockdown or deletion of K^+ channels. For example, gene therapies could target apoptosis-related Kv channels, such as Kv2.1. The other direction is to regulate cell excitability to maintain the balance of input-output in the basal ganglia circuit. For example, therapies could target FS-related genes that control AHPs, such as Kv3.4. Currently these directions are only hypothetical. Future studies are needed to test whether such strategies of gene therapy could be successful.

7. PERSPECTIVES AND FUTURE DIRECTIONS

With the increasing recent discoveries revealing the inner connections between potassium channels and multiple potassium channelopathies (both inherited and acquired disorders), the vital significance of K^+ channels in physiological and pathological processes can not be overemphasized (56, 131-133). Further pursuits for the comprehensive knowledge of structure and functions (involving localization, combinations, regulation) of K^+ channel, combined with the insight of pathology-oriented genetic mechanisms and symptom-induced regulation of K^+ channels, may enable us to select specific candidate genes and to establish therapeutic strategies for PD by targeting at K^+ channels (130, 134-136). We hypothesize that modulating cell viability and improving cell survival and/or regulating cell excitability to maintain the balance of input-output in the basal ganglia circuit may be effective measures to treat PD. We believe that the K^+ channels hold rich promise as therapeutic targets for the treatment of PD, using pharmacological and emerging genetic approaches. However, the efficacy and safety of these treatments in clinical trials remains to be determined, which depends greatly on future studies of K^+ channels and PD pathology.

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