·Minireview·

ATP-sensitive potassium channels: novel potential roles in Parkinson's disease

Jie ZENG[1*], Gang WANG[1*], Sheng-Di CHEN[1,2]

[1]*Department of Neurology and Neuroscience Institute, Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

[2]*Institute of Health Science, Shanghai Institutes of Biological Sciences, Chinese Academy of Science/Shanghai Jiaotong University School of Medicine, Shanghai 200025, China*

Abstract: The ATP-sensitive potassium (K_{ATP}) channels which extensively distribute in diverse tissues (e.g. vascular smooth muscle, cardiac cells, and pancreas) are well-established for characteristics like vasodilatation, myocardial protection against ischemia, and insulin secretion. The aim of this review is to get insight into the novel roles of K_{ATP} channels in Parkinson's disease (PD), with consideration of the specificities K_{ATP} channels in the central nervous system (CNS), such as the control of neuronal excitability, action potential, mitochondrial function and neurotransmitter release.

Keywords: ATP-sensitive potassium (K_{ATP}) channels; Parkinson's disease

1 Introduction

Parkinson's disease (PD) is a most common movement disorder caused by loss of dopaminergic neurons in the substantia nigra pars compacta. For rare forms of familial PD, relevant differences in gene expression have recently been identified (e.g. *α-synuclein*, *parkin*, *UCHL-1*, *PINK1* and *LRRK2*), while any of them can not explain the degeneration especially in the sporadic cases. Many hypotheses for the pathogenesis of sporadic PD have been proposed, including oxidative stress, mitochondrial dysfunction, inflammatory process and apoptosis of dopamine neurons and other related cells in substantia nigra. Nevertheless, the precise etiopathogenesis is not understood. Attempts to avoid side effects of the conventional therapy should aim to identify new targets for potential pharmacological intervention. The ATP-sensitive potassium (K_{ATP}) channels presenting in the control of neuronal excitability, action potential, mitochondrial dysfunction of oxidative stress and neurotransmitter release in the central nervous system (CNS) have been compellingly recognized[1]. Due to their diversity and distinct localizations, the K_{ATP} channels are the interesting candidates for new therapeutic strategies. This review aims to get insight into the novel and crucial roles of K_{ATP} channels in the pathogenesis of PD.

2 Structure and function of K_{ATP} channels

The existence of K_{ATP} channels was initially discovered in cardiac myocytes by Noma in 1983[2] and subsequently identified expressed in pancreatic β cells by Ashcroft in 1990[3]. Then it is proved that K_{ATP} channels present characteristics in different tissues, such as vasodilatation in vascular smooth muscle, myocardial protection against ischemia in cardiac cells, and insulin secretion in pancreas[4]. The basic structure of functional K_{ATP} channels is formed by the heteromeric aggregation of four subunit proteins: each subunit consists of a short amino acid sequence, which forms a "loop" into the membrane, and is flanked by two transmembrane domains. The unit may be supplemented by four additional membrane spanning domains, or two units may be combined to a single protein, thus forming three structural classes of potassium channels[4] (Fig. 1a). As octameric proteins, K_{ATP} channels are heteromultimers of two types of subunits: inward rectifiers,

Corresponding author: Sheng-Di CHEN
Tel: 86-21-64457249
E-mail: chen_sd@medmail.com.cn
*The authors contributed equally to this work.
Article ID: 1673-7067(2007)06-0370-07
CLC number: R363
Document code: A
Received date: 2007-07-24

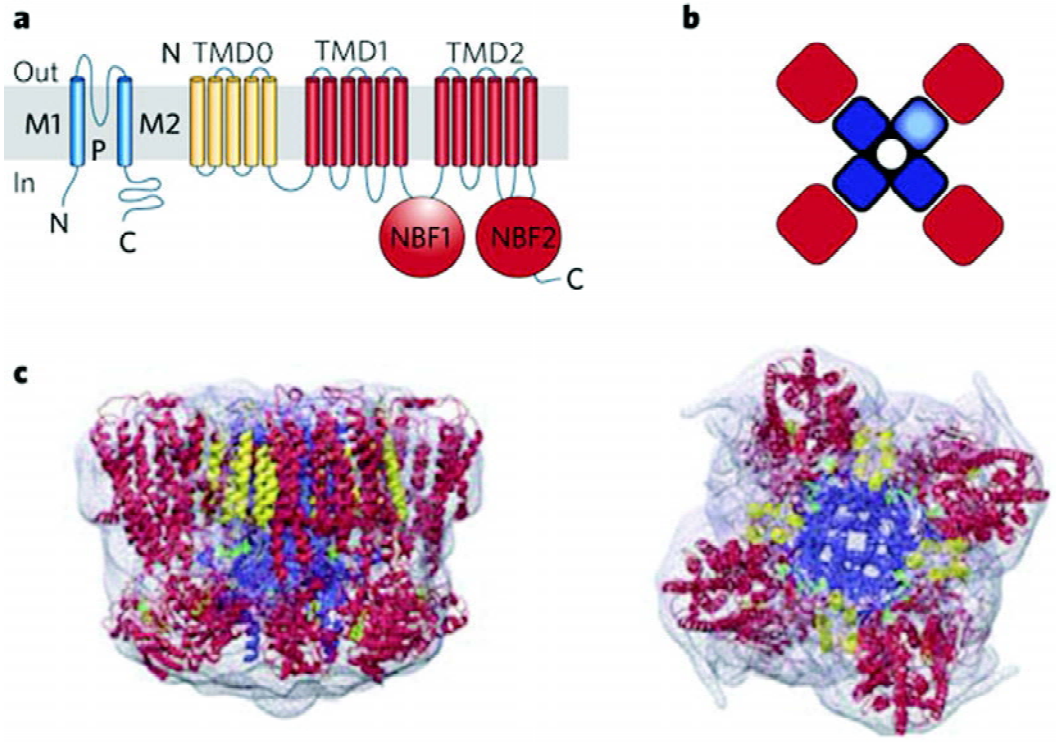

Fig. 1 The K_{ATP} channel is formed from two dissimilar subunits. a, Inward rectifier K^+ channel Kir6 subunits generate the channel pore and sulphonylurea receptor (SUR) subunits generate the regulatory subunit. TMD, transmembrane domain; NBF, nucleotide-binding fold; M1, M2, transmembrane helices; P, pore. b, The channel is a functional octamer of four Kir6 subunits, and each subunit is associated with four SUR subunits. c, Images at 18Å resolution of the entire K_{ATP} complex viewed in the plane of the membrane (left) and from above the membrane (right) require tight packing of subunit models[4].

KIR6.x, members of the Kir6 inwardly rectifying potassium channel family and sulfonylurea receptors, SURs, members of the ATP-binding cassette (ABC) transporter superfamily[4] (Fig. 1b, 1c). Commonly, four pore-forming Kir6 subunits are joined together with four regulatory SUR subunits. However, sometimes the molecular makeup of neuronal K_{ATP} channels also appears to be not homogeneous. Non-proportion of the Kir6.x subunit expression to SUR subunits expression may result in the functional and pharmacological diversity, which will influence the function of neurons, glia, or neuronal networks[5,7,8]. At present, two members of the Kir6 family have been cloned, Kir6.1 and Kir6.2; two SUR isoforms have been identified, SUR1 and SUR2 (SUR2A and SUR2B being the most important). With a combined approach of electrophysiological patch-clamp and single-cell mRNA expression profiling techniques, different combinations of co-expressed K_{ATP} channel subunits have been identified. The mRNA encoding K_{ATP} channels comprising Kir6.2 and SUR1 are abundantly expressed in the nigral dopaminergic neurons with properties similar to those described in pancreatic β cells. Kir6.2 and SUR2A pairs assemble the K_{ATP} channels of cardiac and skeletal muscle, and SUR2B in combination with Kir6.1 subunits generate K_{ATP} channels in smooth muscle. K_{ATP} channel subunits are also widely expressed throughout different brain regions, e.g. in hippocampal pyramidal neurons, locus coerulus and dorsal vagal neurons, striatal interneurons, hypothalamic neurons, and GABAergic and nigral dopaminergic neurons, and there is also evidence for functional presynaptic K_{ATP} channels[6-8].

3 Roles of K_{ATP} channels in PD

Potassium channels are important components of the signal transduction in the nervous system, which are involved in a wide variety of functions such as setting and stabilizing the resting potential of most cell types or regulating the depolarization time course in pacemaker cells. Other parameters, such as action potential duration, firing frequencies, and interspike intervals are also determined by the activity of K_{ATP} channels.

3.1 K_{ATP} channels' responsiveness to ATP/ADP and electrical activity in PD K_{ATP} channels are metabolic sensors

that couple cellular energy metabolism to membrane potential by regulating potassium flux. The primary factor to govern K_{ATP} channel opening is the ATP/ADP ratio: K_{ATP} channels are closed at high ATP-to-ADP ratios and open in response to decreased ATP or increased ADP levels. The explanation was that the decrease in intracellular ADP ($[ADP]_i$) would reduce channel activity (and any increase in intracellular ATP ($[ATP]_i$) would do the same and thus it lead to membrane depolarization and activation of voltage-gated Ca^{2+} channels to increase intracellular Ca^{2+} ($[Ca^{2+}]_i$)[9-11]. By this mechanism, K_{ATP} channel activity exerts a powerful control of cellular excitability. Besides, neuronal K_{ATP} channels are involved in central glucose sensing, neuroendocrining, glucose homeostasis controlling, electrical activity adapting and neuronal ATP consumption. Oweing to the physiological significance in the cell membrane active potential and threshold potential, K_{ATP} channels are important components of the signal transduction of the nervous system and virtually all other cells of the mammalian body[12].

Under the physiological conditions, dopaminergic neurons in the midbrain demonstrate spontaneous action potential firing and, at least in brain slices *in vitro*, most K_{ATP} channels are closed. In the context of metabolic dysfunction in PD, K_{ATP} channels are of special interest for their open probability directly according to the metabolic state of a cell. In mouse PD model induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rapid ATP loss even ATP depletion which has been observed for mitochondrial dysfunction, may contribute to further metabolic disorders and induce the unusual activated open of K_{ATP} channels[11,13].The activation of K_{ATP} might play a neuroprotective role by minimizing metabolic demand in cells, reducing action potential firing rate, and leading to a hyperpolarization of the dopaminergic neurons to loss their normal pacemaker activity. The inactivation of dopaminergic neurons via the potassium conductance could be an appropriate response to reduced energy demand. Additionally, K_{ATP} channel-mediated membrane hyperpolarization will reduce neurotransmitter release, which is helpful for counteracting calcium overload and excitotoxicity. Furthermore, the efflux of K_{ATP}, which is the mechanism of recovering (repolarization), maintaining (clamping) and enhancing (hyperpolarization) the resting potential of the cell, represents a potential safeguard against the deleterious process in PD. The outcome of these effects is a reduction in membrane and cell excitability, which results in a greater cellular resistance to activation by excitatory stimuli. As for the increase of oxygen free radicals, augment of lipoperoxides (LPO) level, and overload of $[Ca^{2+}]_i$, N-methyl-D-aspartate (NMDA) receptor-mediated excitatory toxicity eventually lead to neuronal degeneration[6].Several studies have suggested that cell energy deficiency results in fluctuations in $[ATP]_i$. Regulating K_{ATP} channels through either large changes in the concentration of ATP or through compartmentalization models proposes significant local changes in $[ATP]_i$[9-12].

3.2 K_{ATP} channels are associated with mitochondrial dysfunction in PD Morphological, biochemical, molecular genetic, and cell/animal model studies have suggested that the functions and properties of mitochondria have been identified as a crucial trigger factor in neurodegenerative process of PD[13]. In PD, the dysfunction of the mitochondrial electron transport chain leads to the increase of reactive oxygen species or metabolic stress and renders subsets of selectively vulnerable neurons intrinsically susceptible to cellular degeneration and oxidative stress[12-14]. Mitochondrial K_{ATP} (Mito-K_{ATP}) channels play the roles in controlling the mitochondrial volume, regulating the translation of metabolic status of cells, and responsing open/close channels to injury for neurodegeneration. It is hypothesized that preconditioning of K_{ATP} channels may render neuronal tissues resistant to neurodegenerative process[15]. To test this hypothesis , Tai and Truong *et al.* found that, at the cellular level, activation of K_{ATP} channels in PC12 cells confered protection against mitochondrial complex-I inhibition-induced cell death by rotenone which had been proven to be the pathogenesis of PD[16]. The results suggest that transient activation of K_{ATP} channels can precondition PC12 cells against the neurotoxic effect of a mitochondrial complex I inhibitor. Diazoxide, a mitochondrial K_{ATP} channel selective opener, preconditioned in a dose-dependently way to increase PC12 cell viability, while the protective effect of this preconditioning is attenuated by 5-hydroxydecanoic acid (5-HD), a selective mitochondrial K_{ATP} channel antagonist. In contrast, P-1075, a selective plasma membrane K_{ATP} channel opener, did not show the protective effect. Although plasma K_{ATP} channels are not detected on PC12 cell membrane and only mito-K_{ATP} channels exist on the PC12 mitochondrial membrane, the situation can not be deduced to other types of cells[11,16]. Liu *et al*. had proved that the possible reasons for the protection of K_{ATP} were associated with transcriptional process. Similarly like an

enhanced expression of genes which promote cell survival or a suppressed expression of genes which cause cell death[17]. As the rotenone-induced cell death is associated with cell shrinkage, a distinct feature of apoptosis, meanwhile, surviving cells preconditioned with the mitochondrial K_{ATP} channel opener shows no sign of cell shrinkage, the observed protection may be via the inhibition of apoptotic processes. The protection of K_{ATP} channels on neuronal apoptosis is mediated by increasing mitochondrial Bcl-2 level and decreasing mitochondrial Bax level, a pro-apoptotic member of the Bcl-2 family[18-19].

Other investigations of the protection mechanism of mitochondrial K^+ channel suggest that the opening of mito-K_{ATP} induced by increasing reactive oxygen species (ROS) production combines with blunting mitochondrial Ca^{2+} accumulation, which finally improves the mitochondrial energy production[20]. As hydrogen peroxide (H_2O_2) generate in all cells by mitochondrial respiration, Avshalumov MV examined regulation of K_{ATP} channels in nigral dopaminergic neurons to certain the relationship between H_2O_2 with mito-K_{ATP} channels[21-22]. The observation confirms an essential role of H_2O_2 in activating K_{ATP} channels. It indicates that endogenous H_2O_2 acts in a graded manner to regulate tonic dopaminergic activity and responsiveness to oxidative challenge via K_{ATP} channels. In addition, other intracellular factors like phosphoinositol phosphates (e.g. PIP2), G proteins, or protein kinases could modulate the metabolic sensitivity of K_{ATP} channels as well[13,22]. One has to be highlighted is that the regulation of cell activity by H_2O_2 and metabolic sensitivity of mito-K_{ATP} channels is mainly determined by the alternative expression of SUR subunits. After acute rotenone-induced K_{ATP} channel activation in mouse brain slices, only highly responsive dopaminergic neurons expressing the K_{ATP} channel subunits SUR1 and Kir6.2[20-22]. The other population of dopaminergic neurons in substantia nigra pars compacta (SNpc), which express the other SUR isoform, maintain their pacemaker activity as a response to their partial mitochondrial respiratory chain complex I (CXI) inhibition[13,15,21,23].

3.3 K_{ATP} channels are required in regulation of neurotransmitter release The opening of K_{ATP} channels may result in hyperpolarizing the membrane potential, inhibiting neurotransmitter release, regulating dopamine release in the striatum or glutamate and g-aminobutyric acid (GABA) release in the substantia nigra pars recticulata, and inhibiting glutamatergic transmission in the brain regions(e.g. globus pallidus and substantia nigra pars reticulate) to play critical roles in anti-parkinsonian effects[24]. Previous studies have emphasized that the mechanisms underlying the symptoms of PD involved in the increased GABA transmission in the globus pallidu and the regulation roles of K_{ATP}-like channels of the basal ganglia in dopamine release as well as glutamate and GABA release in the substantia nigra in response to various environmental stimuli[25]. Therefore, the activation of K_{ATP} channels openers in some brain regions(e.g. the corpus striatum, globus pallidus, subthalamic nucleus and substantia nigra), which results in neuron hyperpolarizing, dampening excitability and decreasing transmitter release (including decreasing the K^+-evoked GABA release in pallidal slices), can have anti-parkinsonism effect. Moreover, K_{ATP} channels modulate dopamine (DA) outflow from different slices of the rat caudate nucleus by biochemical study also provides evidence for the role of K_{ATP} channels in the modulation of neurotransmitter release. Two different types of plasmalemmal K_{ATP} channels have been comfirmed: one type with high-affinity binding sites mainly localized on the excitatory neurons, the other with low-affinity binding sites localized on the inhibitory neurons releasing GABA[26].

3.4 K_{ATP} channels are involved in selective vulnerability of SNpc to degeneration The pathological hallmark of PD is the selective degeneration of a subpopulation of dopaminergic midbrain neurons, mainly in the SNpc[1]. The metabolic challenges with parkinsonism-inducing toxins, such as MPTP, cause rapid hyperpolarization and electrical "silencing" of dopaminergic neurons in the substantia nigra, where appears highly vulnerable to the degenerative process, but other areas, e.g. ventral tegmental area (VTA) remain largely unaffected. Liss *et al.* found that adult SN dopaminergic as well as VTA dopaminergic neurons possessed functional K_{ATP} channels with the same molecular make-up. Nevertheless, in the dopaminergic neurons of VTA, K_{ATP} channels were not activated and electrical activity was not altered by inhibition of complex I of the mitochondrial respiratory chain. Interestingly, dopaminergic neurons of VTA area expressed higher levels of uncoupling protein 2 (UCP-2) which may be upstream of K_{ATP} in determining vulnerability of dopaminergic neurons in the substantia nigra[27]. These studies suggest that K_{ATP} channel may eventually help determine whether a dopaminergic neuron lives or dies. In addition, as the degeneration in a subpopulation of dopaminergic neurons in the SNpc of

PD, the brain may adjust to the loss of these cells through increasing activity of remaining cells, which is called "the compensatory mechanisms". The "selectively-escape-system" inner working manner or whether K_{ATP} channels take any part in additional amounts of dopaminergic neurons survival, however, need to be further studied.

To sum up, K_{ATP} channels are well recognized for their ability to couple membrane excitability with cellular energetic status and to be effectors acting as an endogenous defense mechanism against neuronal injury which induced by ATP depletion, oxidative stress, mitochondrial dysfunction and neurochemicals releasing. In addition, the K_{ATP} channel activation can induce the expression of the 70,000 molecular weight class of heat shock proteins(HSP), which act as chaperones to restore the normal functioning of stress-damaged proteins by refolding or reassembling them. Further studies are needed to verify whether HSPs are involved in the K_{ATP} channel-mediated protection against rotenone toxicity[28].

4 Therapeutic targets and potential for PD

Though K_{ATP} channels in the brain do not open under normal conditions, they often serve as a protective mechanism under stress and show significantly up-regulated expression in many pathophysiological conditions, such as in PD and ischemia/hypoxia, which involved in metabolic inhibition. The traditional choice of therapeutic intervention of PD uses dopamine agonists and *L*-dopa (*L*-dihydroxyphenylalanine), which often improve the motor impediments and severe dose-response fluctuations (on-off-phenomenon), hallucinations, uncontrollable dyskinesia, but can not prevent the progress of the disease. Special attention must be paid to avoid above side effects of the conventional therapy, and identify additional targets for potential pharmacological intervention. The utilization of the K_{ATP} channels properties makes a new direction in the pharmacology of ion channels for PD[29]. In accordance with this view, the K_{ATP} channel openers (K_{ATP}COs) which are the novel synthetic molecules and have the ability to induce K_{ATP} potassium conductance, are thought to act as an external factor to improve the opening of K_{ATP} channels. They may offer beneficial effects against metabolic inhibitors to injury which plays a causative role in the etiology of a number of neurodegenerative diseases and are recognized as neuroprotective drugs. Nevertheless, someone hold the opinion that in PD transient K_{ATP} channel activation is a short-term neuroprotective response to metabolic stress, but chronic K_{ATP} channel activation could have fatal consequences for the dopaminergic neurons, in respect that a chronic reduction of neuronal activity and ATP consumption might lead to a reduced expression of some activity-dependent genes (such as neurotrophins) which can promote cell survival[30-31].

ATP-sensitive potassium channels can be attractive candidates for novel therapeutic regimes. The reasons are that the K_{ATP} channels are selectively expressed in nervous structures which are important for pathological changes and neuropsychiatric symptoms of PD. In this case, activation or inhibition of K_{ATP} channels may influence the clinical situation of affected patients. Otherwise, the molecular diversity of the channels should allow the development of highly specific drugs, which may selectively target cell types, groups, or systems throughout the body, correcting or at least improving disturbed functions[32]. In this respect, it is important to understand the regional, cellular, and subcellular localizations of identified ATP-sensitive potassium channel subunits. Consequently, K_{ATP} channels are of meaningful neuropathological features in PD as an indication in the process of neuronal channelopathies and subsequent participation in the propagation of the neurodegeneration, which deserves further pursuit for making comprehensive use of their novel therapeutic potential.

Acknowledgments: This work was supported by grants from the National Natural Science Foundation of China (No. 30700251), the National Basic Research Development Program of China (No.2006CB500706), and the Young Excellent Scholar (2007-2008) Program of Shanghai Jiaotong University School of Medicine.

References:

[1] Wang G, Zhu Y, Kong DH, Chen SD. Some progress about channelopathies. Progress in Physiological Sciences 2004, 35: 251-254. (Chinese, English abstract)

[2] Noma, A. ATP-regulated K^+ channels in cardiac muscle. Nature 1983, 305: 147-148.

[3] Ashcroft SJ, Ashcroft FM. Properties and functions of ATP-sensitive K-channels. Cell Signal 1990, 2: 197-214.

[4] Nichols CG. K_{ATP} channels as molecular sensors of cellular metabolism. Nature 2006, 440: 470-476.

[5] Karschin C, Ecke C, Ashcroft FM, Karschin A. Overlapping distribution of K_{ATP} channel-forming Kir6.2 subunit and the sulfonylurea receptor SUR1 in rodent brain. FEBS Lett 1997,

401: 59-64.

[6] Antcliff JF, Haider S, Proks P, Sansom MS, Ashcroft FM. Functional analysis of a structural model of the ATP-binding site of the K_{ATP} channel Kir6.2 subunit. EMBO J 2005, 24: 229-239.

[7] Thomzig A, Prüss H, Veh RW. The Kir6.1-protein, a pore-forming subunit of ATP-sensitive potassium channels, is prominently expressed by giant cholinergic interneurons in the striatum of the rat brain. Brain Res 2003, 986: 132-138.

[8] Holemans S, Javoy-Agid F, Agid Y, De Paermentier F, Laterre EC, Maloteaux JM. Sulfonylurea binding sites in normal human brain and in Parkinson's disease, progressive supranuclear palsy and Huntington's disease. Brain Res 1994, 642: 327-333.

[9] Minami K, Miki T, Kadowaki T, Seino S. Roles of ATP-sensitive K^+ channels as metabolic sensors: studies of Kir6.x null mice. Diabetes 2004, 53 (Suppl 3): 176-180.

[10] Miki T, Seino S. Roles of K_{ATP} channels as metabolic sensors in acute metabolic changes. J Mol Cell Cardiol 2005, 38: 917-925.

[11] Lamensdorf I, Meiri N, Harvey-White J, Jacobowitz DM, Kopin IJ. Kir6.2 oligoantisense administered into the globus pallidus reduces apomorphine-induced turning in 6-OHDA hemiparkinsonian rats. Brain Res 1999, 818: 275-284.

[12] Hartmann A, Troadec JD, Hunot S, Kikly K, Faucheux BA, Mouatt-Prigent A, *et al*. Caspase-8 is an effector in apoptotic death of dopaminergic neurons in Parkinson's disease, but pathway inhibition results in neuronal necrosis. J Neurosci 2001, 21: 2247-2255.

[13] Yuan H, Zheng JC, Liu P, Zhang SF, Xu JY, Bai LM. Pathogenesis of Parkinson's disease: oxidative stress, environmental impact factors and inflammatory processes. Neurosci Bull 2007, 23: 125-130.

[14] Martin LJ. Mitochondriopathy in Parkinson disease and amyotrophic lateral sclerosis. J Neuropathol Exp Neurol 2006, 65: 1103-1110.

[15] Wu J, Hu J, Chen YP, Takeo T, Suga S, Dechon J, *et al*. Iptakalim modulates ATP-sensitive K^+ channels in dopamine neurons from rat substantia nigra pars compacta. J Pharmacol Exp Ther 2006, 319: 155-164.

[16] Tai KK, McCrossan ZA, Abbott GW. Activation of mitochondrial ATP-sensitive potassium channels increases cell viability against rotenone-induced cell death. J Neurochem 2003, 84: 1193-1200.

[17] Liu D, Lu C, Wan R, Auyeung WW, Mattson MP. Activation of mitochondrial ATP-dependent potassium channels protects neurons against ischemia-induced death by a mechanism involving suppression of Bax translocation and cytochrome *c* release. J Cereb Blood Flow Metab 2002, 22: 431-443.

[18] Tai KK, Truong DD. Activation of adenosine triphosphate-sensitive potassium channels confers protection against rotenone-induced cell death: therapeutic implications for Parkinson's disease. J Neurosci Res 2002, 69: 559-566.

[19] Garlid KD. Cation transport in mitochondria–the potassium cycle. Biochim Biophys Acta 1996, 1275: 123-126.

[20] Nicholls DG, Budd SL. Mitochondria and neuronal survival. Physiol Rev 2000, 80: 315-360.

[21] Avshalumov MV, Chen BT, Koós T, Tepper JM, Rice ME. Endogenous hydrogen peroxide regulates the excitability of midbrain dopamine neurons via ATP-sensitive potassium channels. J Neurosci 2005, 25: 4222-4231.

[22] Avshalumov MV, Bao L, Patel JC, Rice ME. H_2O_2 signaling in the nigrostriatal dopamine pathway via ATP-sensitive potassium channels: issues and answers. Antioxid Redox Signal 2007, 9: 219-231.

[23] Vu CCQ, Bortner CD, Cidlowski JA. Differential involvement of initiator caspases in apoptotic volume decrease and potassium efflux during Fas- and UV-induced cell death. J Biol Chem 2001, 276: 37602-37611.

[24] Milton SL, Lutz PL. Adenosine and ATP-sensitive potassium channels modulate dopamine release in the anoxic turtle (Trachemys scripta) striatum. Am J Physiol Regul Integr Comp Physiol 2005, 289: R77-R83.

[25] Haider S, Antcliff JF, Proks P, Sansom MS, Ashcroft FM. Focus on Kir6.2: a key component of the ATP-sensitive potassium channel. J Mol Cell Cardiol 2005, 38: 927-936.

[26] Steinkamp M, Li T, Fuellgraf H, Moser A. K_{ATP}-dependent neurotransmitter release in the neuronal network of the rat caudate nucleus. Neurochem Int 2007, 50: 159-163.

[27] Liss B, Haeckel O, Wildmann J, Miki T, Seino S, Roeper J. K-ATP channels promote the differential degeneration of dopaminergic midbrain neurons. Nat Neurosci 2005, 8: 1742-1751.

[28] Armstead WM, Hecker JG. Heat shock protein modulation of KATP and KCa channel cerebrovasodilation after brain injury. Am J Physiol Heart Circ Physiol 2005, 289: H1184-H1190.

[29] Neusch C, Weishaupt JH, Bähr M. Kir channels in the CNS: emerging new roles and implications for neurological diseases. Cell Tissue Res 2003, 311: 131-138.

[30] Deutch AY, Winder DG. A channel to neurodegeneration. Nat Med 2006, 12: 17-18.

[31] Lawson K. Is there a role for potassium channel openers in neuronal ion channel disorders? Expert Opin Investig Drugs 2000, 9: 2269-2280.

[32] Lawson K. Potassium channel activation: a potential therapeutic approach? Pharmacol Ther 1996, 70: 39-63.

ATP 敏感性钾通道在帕金森病中的作用

曾洁[1*]，王刚[1*]，陈生弟[1,2]

[1] 上海交通大学附属瑞金医院神经内科 / 神经病学研究所，上海 200025

[2] 中国科学院上海生命科学研究院 / 上海交通大学医学院健康科学研究所，上海 200025

摘要：ATP 敏感性钾通道已被证实广泛分布于血管平滑肌、心肌、胰腺等组织，发挥着诸如血管舒张、心肌缺血的保护及胰岛素分泌等作用。本综述旨在阐明ATP敏感性钾通道在帕金森病发病机制中参与调控神经元电兴奋性、线粒体功能及神经递质释放的独特角色，以揭示对其进行深入研究的意义及作为帕金森病治疗靶点的可能性和潜在价值。

关键词：ATP 敏感性钾通道；帕金森病