

Review

Neuroprotective role of ATP-sensitive potassium channels in cerebral ischemia

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ATP-sensitive potassium (K_{ATP}) channels are weak, inward rectifiers that couple metabolic status to cell membrane electrical activity, thus modulating many cellular functions. An increase in the ADP/ATP ratio opens K_{ATP} channels, leading to membrane hyperpolarization. K_{ATP} channels are ubiquitously expressed in neurons located in different regions of the brain, including the hippocampus and cortex. Brief hypoxia triggers membrane hyperpolarization in these central neurons. *In vivo* animal studies confirmed that knocking out the Kir6.2 subunit of the K_{ATP} channels increases ischemic infarction, and overexpression of the Kir6.2 subunit reduces neuronal injury from ischemic insults. These findings provide the basis for a practical strategy whereby activation of endogenous K_{ATP} channels reduces cellular damage resulting from cerebral ischemic stroke. K_{ATP} channel modulators may prove to be clinically useful as part of a combination therapy for stroke management in the future.

Keywords: ATP-sensitive potassium channel (K_{ATP}); Kir6.2; SUR subunit; stroke; nociception; neuropathic pain; neuroprotection

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Introduction

Potassium (K^+) channels are the most ubiquitously distributed ion channels and are found virtually in all types of cells^[1, 2]. Because K^+ ions have a negative equilibrium potential across the cell membrane, the opening of K^+ channels stabilizes the membrane potential by hyperpolarizing the cell closer to the K^+ equilibrium potential (E_K). Thus, K^+ channels play a major role in setting the resting membrane potential and the duration of action potentials. These channels also play a role in repetitive firing frequency, thereby suppressing the excitability of a cell^[1, 2]. Selective K^+ permeability was originally described in nerve cells^[3, 4]. To date, more than 80 genes for K^+ channel subunits have been identified in mammalian cells, and multiple K^+ channel subtypes are expressed in a single cell to control its K^+ permeability^[1, 2]. Inwardly rectifying K^+ (Kir) channels conduct the inward rectifier current, thus hyperpolarizing the membrane potential^[5].

Adenosine triphosphate (ATP)-sensitive K^+ (K_{ATP}) channels are members of the Kir superfamily and were originally described in the heart^[6]. These channels were later identified in many other tissues, including the skeletal muscle^[7], smooth

muscle^[8], brain^[9–12], pituitary gland^[13, 14], kidney^[15], and in pancreatic beta cells^[16–19]. K_{ATP} channels conduct inward-rectifier potassium currents that are inhibited by intracellular ATP and couple the cellular metabolic status to the electrical activity of the cell membrane^[6, 16, 20, 21]. An increase in the ATP/ADP ratio closes K_{ATP} channels (leading to depolarization), whereas a decrease in the ATP/ADP ratio opens K_{ATP} channels (leading to hyperpolarization). Thus, K_{ATP} channels modulate many of the cellular events and functions under physiological and pathophysiological conditions. Recently, it has been proposed that K_{ATP} channels are one of the non-glutamate mechanisms for stroke^[22, 23]. Broad reviews of K_{ATP} channels in the heart^[21, 24] and pancreatic cells^[20, 21, 25] have been presented elsewhere. The specific role of K_{ATP} channels in the neurovascular unit in stroke has also been recently reviewed^[26]. This review focuses on neuronal K_{ATP} channels and the neuroprotective role of K_{ATP} channels in cerebral ischemia.

General description of K_{ATP} channels

K_{ATP} channels are heteromultimers of Kir6 and sulfonylurea receptor (SUR) subunits^[27] (Figure 1). They are activated by energy depletion and conduct a weak inwardly rectifying K^+ current, thus playing important roles in the regulation of cellular function by linking cellular metabolism to the electrical activity of cell membranes^[20, 27–29] (Figure 2).

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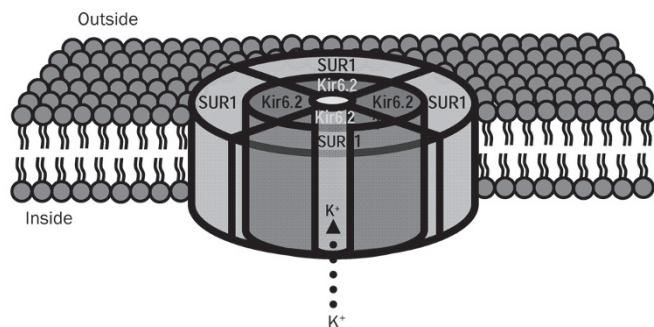


Figure 1. A schematic illustration showing the proposed structure of a K_{ATP} channel in neurons. The K_{ATP} channel is a hetero-octamer comprising two subunits: four pore-forming Kir6.2 subunits and four regulatory sulfonylurea receptor (SUR) subunits.

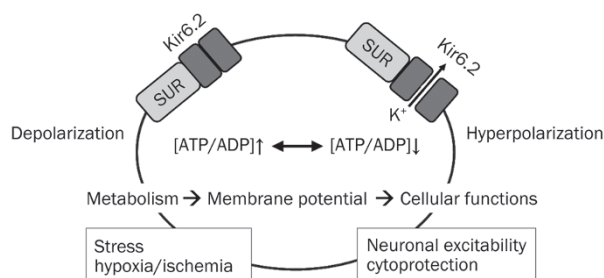


Figure 2. Schematic illustration of K_{ATP} channels function in neurons. K_{ATP} channels serve as metabolic sensors to couple electrical activity of neurons. Under normal physiological conditions, K_{ATP} channels remain closed due to the high ATP/ADP ratio. Reducing the ATP/ADP ratio by either decreasing ATP levels or enhancing ADP levels opens the channel and allows K^+ ions to exit the cells, thus hyperpolarizing the neurons. SUR, sulfonylurea receptor.

K_{ATP} channel genes

The Kir6 subfamily is a member of the weak inward rectifier family and has two members, Kir6.1 and Kir6.2. The Kir6.2 gene (KCNJ11) in humans is located on chromosome 11. Kir6.2 was cloned from a human genomic library and shares 96% amino acid identity with mouse and rat Kir6.2^[30]. Kir6.1 genes (KCNJ8) are mainly expressed in the mitochondria^[12, 31, 32]. Two SUR subunits, SUR1 and SUR2, have been identified as the regulatory subunits of K_{ATP} channels^[33]. The SUR1 subunit is encoded by the ABCC8 gene, which is located on chromosome 11p15.1 and is mainly found in pancreatic beta cells and neurons^[33–35]. The SUR2 subunit is encoded by the ABCC9 gene, which is located on chromosome 12p12.1 and is expressed mainly in the heart and skeletal muscles, as well as in some neurons^[5, 36]. SUR2 has two alternative splice variants, SUR2A and SUR2B, which have major differences in the last 42 C-terminal amino acid residues (C42)^[37]. The C42 of SUR2B shows a higher homology to the C42 of SUR1^[37].

Structure of functional K_{ATP} channels

K_{ATP} channels are heteromultimers of the Kir6 and SUR sub-

units. These subunits are in a 1:1 ratio of stoichiometry. The Kir6 subunit is the pore-forming subunit of K_{ATP} channels^[30, 38]. Kir6.2 mediates the inhibitory effect of ATP on the K_{ATP} channels. The SUR subunits are members of the ATP-binding cassette (ABC) protein superfamily^[39]. The SUR subunits are sensitive to the adenine nucleotides, Mg-ADP^[20, 27, 29, 40]. Reducing the intracellular concentration of ATP or the ATP/ADP ratio gates the K_{ATP} channel.

A functional K_{ATP} channel is assembled by four Kir6.x and four SUR subunits, forming a hetero-octameric complex (SUR/Kir)₄. The functional diversity of the K_{ATP} channels results from the assembly of different subtypes of the Kir6.x and SUR subunits. Kir6.1 genes are mainly expressed in the mitochondria. Kir6.1-based channels have a smaller unitary conductance than Kir6.2 subtype channels^[27]. Kir6.2 subunits are found in plasmalemmal membranes (cell surface membranes)^[12, 20, 27, 29, 32]. Most functional K_{ATP} channels contain the Kir6.2 subunit; thus, the heterogeneity observed between different K_{ATP} channels mainly arises from the differential expression of the SUR regulatory subunits. SUR1- and SUR2-based channels are differentiated by their selective sensitivity to sulfonylureas drugs (such as glibenclamide), whereas SUR2A- and SUR2B-based channels are differentiated by their selective affinity to diazoxide^[27].

Gating properties

K_{ATP} channels exhibit fast and long interburst closing kinetics^[41–43]. The fast gating kinetics of the channels is determined by an intrinsic structure within the pore-loop that is near the selectivity filter of the Kir6.2 subunit^[41, 44]. The long last interburst closing kinetics requires ATP binding to the TM2 helices^[42, 45]. The conformational modeling describes one open and multiple closed states of the channel^[36, 43]. A current conducting channel requires all four Kir6.2 subunits in the open conformation, and ATP binding to any one of the four subunits will shift the channel to a closed state. SUR subunits are considered the gatekeepers of the ATP-inhibited Kir6.2 pores because they couple their N-terminal bundle of five transmembrane helices (TMD0-L0) to the outer helix and N-terminus of Kir6.2. This coupling bidirectionally modulates channel gating^[34, 46].

Nucleotide sensitivities of K_{ATP} channels

K_{ATP} channels have distinctive sensitivities to the nucleotides ATP and ADP^[27]. ATP binds to the cytoplasmic domain of the Kir6.2 subunit^[44, 47, 48] to inhibit the channel^[49]. Each Kir6.2 subunit provides one ATP binding pocket, which is constituted by residues R50, I182, K185, R201, and G334^[5, 36]. The interference of ATP binding releases channel inhibition and results in channel activation^[5, 36]. Mg-ADP is the endogenous activator of K_{ATP} channels via the SUR regulatory subunits^[5]. Each SUR subunit has two nucleotide binding domains (NBD1 and NBD2) and 17 putative transmembrane domains, including an N-terminal hydrophobic region (TMD0) containing five TM helices and two repeats of six TM helices (TMD1 and TMD2). The NBDs are found with the Walker A and Walker

B motifs, which are located at the large cytosolic loops following the TMD1 and TMD2 repeats. Dimerization of the two NBDs generates the catalytic sites for ATP hydrolysis and thus is essential for transducing the effect of ADP to Kir6.2^[50–52]. Mutations that disrupt NBD dimerization reduce the ADP-mediated activation of K_{ATP} channels^[49]. These mutations include G1479R^[40, 53] in the NBD2 of SUR1 and V187D^[54] in the TMD0 of SUR1. Under normal physiological ATP levels, the probability that there will be open K_{ATP} channels is less than 0.1% if SUR regulatory subunits are absent^[15, 36].

Pharmacology

SUR subunits are major pharmacological targets. K_{ATP} channels have distinctive pharmacology^[27]. Sulfonylureas are a type of potassium channel blocker that works by binding to SUR subunits^[27, 55]. The most common sulfonylureas include glibenclamide, acetohexamide, tolbutamide, glipizide, and glimepiride. A single serine residue (S1237) located at the C-terminus of the TMs of the SUR1 subunit is critical for the high affinity binding ($K_i=2\text{ }\mu\text{mol/L}$) of tolbutamide and glibenclamide to Kir6.2/SUR1 K_{ATP} channels^[56]. A bivalent structure in the glibenclamide binding site requires the cytoplasmic loop 3 (between TM5 and TM6) and cytoplasmic loop 8 (between TM15-TM16) regions of the SUR1 subunit^[57]. The low affinity binding site ($K_i=1.8\text{ mmol/L}$) for tolbutamide is located on Kir6.2^[58].

K_{ATP} channels can be activated by a group of drugs called potassium channel openers. These drugs include diazoxide, cromakalim, pinacidil, nicorandil and minoxidil sulfate. Diazoxide binds to SUR1 subunits and enhances K⁺ efflux through the Kir6.2/SUR1 channels in pancreatic beta-cells, resulting in cell membrane hyperpolarization^[59]. In contrast, the drugs pinacidil, nicorandil and cromakalim have a high sensitivity to Kir6.2/SUR1 channels, thus leading to stronger effects on the Kir6.2/SUR2A subunits of cardiac K_{ATP} channels^[24, 60]. The binding site for cromakalim, pinacidil and nicorandil is located within the TM2 domain of SUR2. The nucleotides L1249 and T1253 in SUR2A and T1286 and M1290 in SUR2B are necessary and sufficient for the channel opener effects^[61–63]. K_{ATP} channels in smooth muscle respond to all of these drugs. Recently, several new K_{ATP} channel openers, such as iptakalim, have been developed. Iptakalim showed cytoprotective effects^[64] via activating the SUR subunits^[65]. However, it is unknown whether iptakalim acts by regulating Kir6.2-K_{ATP} and/or mitoK_{ATP} channels^[66].

Cellular regulation of K_{ATP} channels

K_{ATP} channel activity is regulated by phosphatidylinositol 4,5-bisphosphate (PIP₂) via interaction with the cytoplasmic domain that is close to the ATP binding site of Kir6.2 (including residues R54, R176, R177, and R206)^[28, 67, 68]. PIP₂ decreases the ATP sensitivity of the channels by preventing the channel from closing, thus stabilizing the open state. K_{ATP} channel activity is also regulated by protein kinase A (PKA) in smooth muscle cells^[69, 70] and cytoskeletal actin in the cardiac

atrium^[71]. K_{ATP} channel activity is suppressed by a SNARE protein, syntaxin 1A, via protein-protein interactions with the SUR subunits^[72–75]. Syntaxin 1A decreases the activity^[76] and the membrane expression level of K_{ATP} channels^[77]. Syntaxin 1A binding to the SUR1 subunit also attenuates the effect of K⁺ channel openers, such as diazoxide, NNC55-0462, P1075, and cromakalim^[78, 79].

K_{ATP} channels in the central nervous system

K_{ATP} channels are extensively expressed in various regions of the mammalian brain^[9, 11, 80], including the substantia nigra (SNr)^[81, 82], neocortex^[83], hippocampus^[84], and hypothalamus^[85, 86]. They have been detected in many cell types, such as glial cells^[84, 87] and neurons in the hippocampus^[88], dorsal vagus^[89], hypothalamus^[85, 86, 90], and SNr^[91]. Single cell RT-PCR analysis showed that Kir6.2 mRNA is predominantly expressed in interneurons and pyramidal, granule and neuroglial cells of the hippocampus in the brains from young rats aged 10–13 d^[84]. In the adult brain, Kir6.2 subunits have been found in hippocampal^[87, 92], cortical^[93], and hypothalamic neurons^[94], as well as in the SNr pars reticulata^[95]. Immunohistochemical studies showed that Kir6.2 subunits are mainly located in the somata and dendrites of the central neurons^[92, 93, 96]. Mitochondrial K_{ATP} channels are also found in the rat brain, and the expression level of Kir6.1 (per milligram of mitochondrial protein) is six to seven times higher than that in the heart and liver^[12]. Radioligand binding studies showed that regional expression of K_{ATP} channels in the brain showed different affinities to sulfonylureas^[97].

Function of neuronal K_{ATP} channels

K_{ATP} channels in the hypothalamus play a critical role in glucose homeostasis by regulating the secretion of counter-regulatory hormones, including glucagon and catecholamines, via the autonomic nervous system^[98]. However, the primary role of K_{ATP} channels in many other central neurons is not glucosensing^[84, 90, 99]. For instance, basal activity of K_{ATP} channels can affect neuronal excitability in non-glucosensing neurons^[100, 101]. In the dentate granule neurons in the mouse hippocampus, K_{ATP} channels are expressed with a high density^[84, 99]. The single channel conductance of K_{ATP} channels is suppressed by strophanthidin, which is a blocker of the Na⁺-K⁺ ATPase. Moderate action potential firing can evoke K_{ATP} channel opening via Na influx and ATP depletion. The ketone body R-beta-hydroxybutyrate can enhance neuronal electrical activity by opening K_{ATP} channels^[102]. Similarly, single channel recordings in brainstem inspiratory neurons show that bursts of single K_{ATP} channel openings are in synchrony with the respiratory firing rhythm. The probability of open channels (P_{open}) is increased by approximately 60% after a strong burst of action potentials^[103]. Blocking the Na⁺-K⁺ ATPase reduces the increased P_{open} of K_{ATP} channels. Thus, ATP consumption in response to Na⁺ influx from action potentials regulates the opening of K_{ATP} channels under physiological conditions.

K_{ATP} channels in dorsal root ganglia (DRG) neurons may involve nociception and neuropathic pain

K_{ATP} channels are also expressed in DRG neurons^[104, 105]. The subunits Kir6.2, SUR1 and SUR2, but not Kir6.1, are identified in the DRG neurons using immunohistochemistry and electrophysiology^[104, 105]. The neuronal injury in axotomy decreases the K_{ATP} channel current in the primary afferent neurons in the DRG, which is mediated by CaMKII^[106]. The suppressed K_{ATP} channels in axotomized DRG neurons are still responsive to the K_{ATP} channel blocker glibenclamide and opener diazoxide. In addition, K_{ATP} channels are activated by CaMKII activators. The neuroprotective role of these CaMKII-dependent K_{ATP} channels may inhibit excitotoxic cell injury. K_{ATP}-mediated neuroprotection may be suppressed in axotomy. Thus, opening of the DRG neuronal K_{ATP} channels decreases neuronal excitability, inhibits neurotransmission and possibly suppresses hyperalgesia. The K_{ATP} channels in the DRG neurons are potential therapeutic targets for antihyperalgesia in neuropathic pain.

K_{ATP} channels in the forebrain involving neuroprotection against seizure

Overexpression of SUR1 in the forebrain, including the cortex, hippocampus and striatum, results in resistance to kainic acid-induced seizures^[107]. Mice that overexpress SUR1 exhibit normal brain anatomy and morphology, as well as normal locomotor and cognitive behaviors. The regional transgenic overexpression of the SUR1 subunit of K_{ATP} channels in the forebrain protects mice against kainic acid-induced seizure and hippocampal neuronal cell death. This observation indicates that the neuronal K_{ATP} channels are important mediators of neuroprotection in the brain and may have potential applications in protecting neurons against hyperexcitability and excitotoxicity during seizure and epileptic insults.

K_{ATP} channels in the substantia nigra region involving neuroprotection against hypoxia-induced seizures

The SNr plays a crucial role in the propagation of seizures^[108], which can be evoked by insults such as hypoxia and hypoglycemia. The K_{ATP} channels expressed in the SNr region are composed of the Kir6.2/SUR1 subunits^[109], which display high affinity binding to sulfonylureas^[97, 110]. K_{ATP} channels are predominantly expressed in GABAergic neurons^[11]. A decrease in glucose levels leads to the opening of presynaptic K_{ATP} channels and suppression of GABA release^[11]. K_{ATP} channels are involved in protecting the brain against seizures and mediating ischemic preconditioning in the brain^[11]. A brief hypoxia (90 s) hyperpolarizes the membrane potential and decreases the firing rate by 30% in wild-type SNr neurons. In contrast, hypoxic conditions depolarize the membrane potential and increase the firing rate in the Kir6.2^{-/-} neurons, suggesting that the K_{ATP} channel-mediated suppressive effect on SNr activity is sufficient to reverse hypoxia-induced superactivity of the neurons. In addition, neurons deficient for Kir6.2 show more susceptibility to hypoxic damage than their wild-type counterparts^[95]. The Kir6.2^{-/-} mice exhibit generalized seizures

in response to the same period of hypoxia, whereas wild-type mice revive normally^[95]. K_{ATP} channels suppress the neuronal activity in the SNr. This suppression may determine the seizure threshold under hypoxic conditions^[95]. SUR1^{-/-} mice also exhibit hypersensitivity to hypoxic insult^[111]. Thus, the K_{ATP} channels in SNr neurons act as a metabolic sensor to mediate hypoxic hyperpolarization, and in turn, prevent seizure propagation during hypoxic stress. This may have implications in human epilepsy^[112, 113].

K_{ATP} channels and their neuroprotective role in cerebral ischemia

Similar to that observed in cardiac ischemia^[55, 60, 114], a neuroprotective role of K_{ATP} channels has also been suggested in focal and global ischemia models twenty years ago^[115]. K_{ATP} channels in a large number of central neurons remain closed, except under conditions of severe metabolic deprivation, such as anoxia or ischemia (Figure 2).

Activation of mitochondrial K_{ATP} channels initiates ischemic pre-conditioning and prevents the mitochondrial dysfunction associated with Ca²⁺ overload during ischemic reperfusion in the heart^[116-118]. In adult animals, application of mitochondrial K_{ATP} openers, such as diazoxide or BMS-191095, reduces neuronal death (rats: ^[116, 119-121]; mice: ^[122]), whereas a selective mitochondrial K_{ATP} channel blocker, 5-hydroxydecanoate, prevents preconditioning-induced neuronal protection in middle cerebral artery occlusion (MCAO) focal cerebral ischemia^[123]. In contrast, xenon-induced preconditioning is not associated with the mitochondrial channels, but rather, is mediated by plasmalemma K_{ATP} channels^[124]. The mechanisms underlying the mitochondrial K_{ATP} channel-related neuroprotective effects remain unclear. However, SUR1 subunits may not be directly involved because adult SUR1 knockout mice exhibit preconditional ischemic tolerance^[124].

Activation of the plasmalemmal K_{ATP} channels hyperpolarizes neurons (Figure 3) and may stabilize the resting membrane potential during ischemic insults and stress^[125], which, in turn, can protect neurons against neuronal damage and neurodegeneration that is caused by anoxic membrane depolarization and excitotoxicity^[115, 126]. Expression of K_{ATP} channel

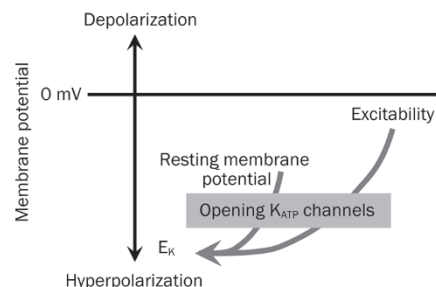


Figure 3. Opening of K_{ATP} channels lead to K⁺ ion efflux and hyperpolarization of the cell membrane, resulting in a decrease in cell excitability. This hyperpolarization occurs by making the membrane potential more negative, which brings it towards the potassium equilibrium potential (E_K). Hyperpolarization suppresses and inhibits cell excitability.

genes and proteins have been detected by PCR^[84] and immunohistochemistry in different neuronal populations in the hippocampus of adult rats^[87]. K_{ATP} channels are preferentially expressed in the interneurons, CA3 neurons, and granule cells that are resistant to ischemic injury, especially in global ischemia^[127, 128]. However, the underlying mechanism is not yet understood.

Under normal physiological conditions, neuronal K_{ATP} channels are presumably closed due to high intracellular ATP levels (Figure 2). During the initial phase of hypoxia and ischemia, energy failure reduces the ATP/ADP ratio, which activates neuronal K_{ATP} channels, causing hyperpolarization of the neuronal cell membrane and suppression of neuronal activity (Figure 2). Similar to previous reports^[88, 95, 129, 130], we reported that membrane hyperpolarization was induced during the first 5 min of ischemia in both hippocampal and cortical neurons^[92, 93]. Using Kir6.2 knockout mice, we further reported that hippocampal CA1 neurons that were deficient for Kir6.2 revealed rapid depolarization and increased neuronal activity in response to hypoxia. In contrast, neuronal suppression occurred in wild-type neurons under similar conditions^[92]. Hypoxic hyperpolarization in wild-type hippocampal CA1 neurons could be prevented by the K_{ATP} channel blocker tolbutamide. Depending on the length of the hypoxic challenge, wild-type neurons initially demonstrate hypoxic hyperpolarization, which is then followed by speedy recovery and stabilization of the cell membrane potential. Our *in vivo* study also showed that cortical neurons lacking the Kir6.2 gene are more vulnerable than wild-type neurons to ischemic insults by middle cerebral artery occlusion^[93]. Our findings provide the first convincing evidence that Kir6.2 containing K_{ATP} channels are important for neuroprotection against cerebral ischemia.

An independent group, using knock-in (KI) mice overexpressing Kir6.2-containing K_{ATP} channels, further confirmed the crucial role of Kir6.2 in neuroprotection against hypoxia-ischemia^[131]. Specifically, overexpression of Kir6.2 reduced the spontaneous electrical activity recorded in hippocampal and cortical neurons. In this study, the resting membrane potentials for both animals were not described. In response to hypoxia-ischemia challenge, the infarction in Kir6.2 overexpressing animals was smaller compared to that of the wild-type animals. The findings using overexpression of Kir6.2 in Kir6.2 KO mice strongly support the notion that Kir6.2 is neuroprotective against ischemia.

In addition to neurons, K_{ATP} channels are also found in astrocytes and microglial cells. Recent studies show that the SUR1 receptor is upregulated in response to pro-inflammatory signals, and the K_{ATP} channel blocker, glibenclamide, exerts neuroprotective effects through its action on non-neuronal cells in the MCAO model in rat^[132, 133]. Because glibenclamide also has non- K_{ATP} channel effects, mechanisms underlying the effect of glibenclamide remain to be further investigated.

Summary and therapeutic aspects

Kir6.2 of K_{ATP} channels is ubiquitously expressed in the brain. Studies using Kir6.2 knock-in or knock-out mouse models

indicate that the opening of K_{ATP} channels shifts the cell membrane potential more negatively (hyperpolarization) towards the E_K , leading to suppression of neuronal activity and excitability. Thus, opening K_{ATP} channels under metabolic stress can protect neurons against neuronal injury during cerebral ischemia and stroke. While the functional roles of Kir6.1, SUR1 and SUR2 in neuroprotection necessitate further evaluation, it has been suggested that K_{ATP} channels may be involved in the remodeling of neurovascular units in stroke^[26]. Kir6.2-containing K_{ATP} channels regulate the membrane potential and contribute to the pathophysiological hyperexcitability of neurons induced by hypoxia and ischemia incidents. Thus, Kir6.2-containing K_{ATP} channels may have therapeutic potential as a target for stroke. It is anticipated that K_{ATP} channel modulators will be useful in the treatment of stroke.

Abbreviations

ABC, ATP-binding cassette protein; ABCC8, ATP-binding cassette C8 gene; CaMKII, calmodulin kinase II; DRG, dorsal root ganglia; K_{ATP} , ATP sensitive potassium channels; KCN, gene name for potassium channel; KCNJ11, potassium channel J11 gene; Kir, inward rectifier potassium channels; MCAO, middle cerebral artery occlusion; NBD, nucleotide binding domain; PIP2, phosphatidylinositol 4,5-bisphosphate; RT-PCR, reverse transcription polymerase chain reaction; SNr, substantia nigra; SUR, sulfonylurea receptor; TM, transmembrane region; TMD, transmembrane domain.

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