Review Article

The role of $K_{\text{ATP}}$ channels in cerebral ischemic stroke and diabetes

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Abstract

ATP-sensitive potassium ($K_{\text{ATP}}$) channels are ubiquitously expressed on the plasma membrane of cells in multiple organs, including the heart, pancreas and brain. $K_{\text{ATP}}$ channels play important roles in controlling and regulating cellular functions in response to metabolic state, which are inhibited by ATP and activated by Mg-ADP, allowing the cell to couple cellular metabolic state (ATP/ADP ratio) to electrical activity of the cell membrane. $K_{\text{ATP}}$ channels mediate insulin secretion in pancreatic islet beta cells, and controlling vascular tone. Under pathophysiological conditions, $K_{\text{ATP}}$ channels play cytoprotective role in cardiac myocytes and neurons during ischemia and/or hypoxia. $K_{\text{ATP}}$ channel is a hetero-octameric complex, consisting of four pore-forming Kir6.x and four regulatory sulfonylurea receptor SURx subunits. These subunits are differentially expressed in various cell types, thus determining the sensitivity of the cells to specific channel modifiers. Sulfonylurea class of antidiabetic drugs blocks $K_{\text{ATP}}$ channels, which are neuroprotective in stroke, can be one of the high stroke risk factors for diabetic patients. In this review, we discussed the potential effects of $K_{\text{ATP}}$ channel blockers when used under pathological conditions related to diabetics and cerebral ischemic stroke.

Keywords: potassium channels; $K_{\text{ATP}}$ channels; $K_{\text{ATP}}$ channel blockers; sulfonylurea; stroke; diabetes

Introduction

Stroke and diabetes are currently the most common causes of death and the leading causes of chronic disability in the world. Diabetes is associated with higher risk of stroke. Both stroke and diabetes cause significant social and economic impacts worldwide. Thus, further understanding of stroke in diabetes can help to prevent occurrences and develop new therapeutic targets, which are priorities for stroke research.

Stroke is characterized by inadequate oxygen, blood and nutrient supply to the brain due to a vascular event, either a cerebrovascular clot or rupture. There are three main types of stroke, ischemic (commonly caused by vessel blockage), hemorrhagic (caused by vessel rupture) and transient ischemic attack (caused by temporary vessel blockage). Poor blood flow or bleeding in the brain due to stroke can result in neuronal death and rapid loss of cognitive and physical functions, which may be permanent. In ischemic stroke, recombinant tissue plasminogen activator (rtPA) can be used during a limited window of time immediately following the stroke insults to dissolve the blood clot and reduce the severity of the stroke damage in the brain, however, there is currently no other effective treatment for stroke. Therefore, taking prophylactic measures is the most effective strategy.

Diabetes mellitus is a group of metabolic disorders with persistent hyperglycemia that may be fatal if not managed appropriately. There are three main types of diabetes including type 1, type 2 and gestational diabetes. Persistent hyperglycemia in diabetes mellitus is caused by hypoinsulinemia and/or insulin insensitivity as a result of pancreatic beta-cell failure or periphery insulin resistance, diabetes is as a result of both genetic and environmental factors$^{[1]}$. Serious long-term diabetic complications include stroke, heart disease, foot ulcers, nephropathy, retinopathy and neuropathy. Diabetes and its common comorbidities include hypertension, high blood cholesterol, atherosclerosis, atrial fibrillation and obesity, all of which independently contribute to increasing the risk for stroke$^{[2]}$. As many as 43% of patients admitted for acute ischemic stroke have undiagnosed diabetes$^{[3]}$. Diabetes is considered as a major independent risk factor for stroke that is...
consistently observed in multiple racial backgrounds\textsuperscript{[4-6].} Both ischemic and hemorrhagic stroke risk are demonstrated in diabetics\textsuperscript{[7,8]}, however this review is focused on ischemic stroke which is more common in diabetics.

**Diabetes and cerebral ischemic stroke**

Diabetes increases stroke risk through a multitude of different mechanisms including high HbA1c, microvascular complications and low HDL cholesterol\textsuperscript{[9].} Under Medicare in the United States, one stroke event costs $22,657 initially and up to $2488 per month thereafter for up to a year\textsuperscript{[10].} A projected 439 million individuals will suffer from diabetes by 2030 and with it carry dramatically higher risks for limb amputations, vision loss, heart disease and stroke complications\textsuperscript{[11].} Without an effective treatment to reverse stroke damage, prevention remains the best option. Diabetes induces changes in all aspects of the neurovascular unit, increasing vascular disease risk and impairing functional recovery from ischemic events. Presently, the most effective preventative measures are intensive blood glucose, blood pressure and blood lipid control\textsuperscript{[12-14].} Hyperglycemia and hypoinsulinemia are detrimental to brain function. Acute and long-term complications can be minimized with adequate glycemic control through diet and exercise, insulin injections and/or oral medications. Diabetes and hyperglycemia cause more severe stroke outcomes\textsuperscript{[15-18]}, and therefore glycemic control is extremely important for stroke prevention. The correlation between hyperglycemia, diabetes, increased stroke risk and poorer post-stroke outcomes is very well established\textsuperscript{[19-27].}

**Neuron**

Diabetes is associated with many different types of neuropa-thy. Prolonged hyperglycemia causes periphery (impaired sensation in extremities), autonomic (disrupted autonomic control), proximal (pain and weakness in limbs) and focal neuropathy (sudden weakness of one nerve). Most diabetic neuropathies are closely linked to microvascular injury, however there are various suggested mechanisms forming a direct link from hyperglycemia, hypoinsulinemia and insulin resistance to nerve damage. High levels of glucose can cause excessive influx of sugar alcohols, excessive free radical stress, loss of cytoskeletal proteins, and lack of up-regulation of axon repair proteins upon nerve injury\textsuperscript{[28-32].} In the case of diabetic stroke, hyperglycemia overloads anaerobic energy production causing stress on neurons and can exacerbate any calcium imbalances and ROS accumulation therefore leading to increased cell death upon ischemic injury\textsuperscript{[33].} Further, stroke in diabetes induces epigenetic down-regulation of neuron-specific enolase and neuronal nitric oxide synthase as compared to non-diabetic stroke\textsuperscript{[34].} Neuron-specific enolase is implicated in synapse formation and its release into serum is a biomarker for stroke\textsuperscript{[35,36].} Post-ischemic hyperglycemia enhances sodium-glucose transporter 1 and exacerbates neuronal damage\textsuperscript{[33].} Hence, strict glycemic control in diabetes reduces the incidence of diabetic neuropathy.

**Cerebrovascu-lature and endothelia**

The vasculature is essential to neuronal function as it is responsible for delivery of nutrients and removal of metabolites. Any impairment/damage to vasculature due to diabetes can have detrimental effects on neurological health especially in the event of ischemic injury. Prolonged hyperglycemia induces vascular changes, ranging from microvascular (retinopathy) to macrovascular (atherosclerosis) and leads to hypoperfusion/hypoxia. Diabetes leads to endothelial dysfunction causing poor structural integrity of vessel walls, arterial stiffening causing increase risk for vessel damage and systemic inflammation ultimately leading to atherosclerosis (risk factor for stroke) and stroke\textsuperscript{[19].} Hyperglycemia reduces available NO vasodilator, reducing perfusion to brain, intensifying inflammatory response and edema further increasing cell death post-stroke\textsuperscript{[34,37].} Further, STZ-diabetes induces S-glutathionylation of Kir6.1, reducing number of functional K\textsubscript{ATP} channels, impairing vasodilation in heart, kidney and mesenteric rings. Similar studies have not been done to confirm effects in cerebrovasculature\textsuperscript{[38,39].} In ischemia conditions, intranasal insulin injections have been proven beneficial for acute events\textsuperscript{[40,41]. In addition, hyperglycemia induces down-regulation of microRNA223 and -146a leading to platelet activation and increased risk for stroke in diabetic patients\textsuperscript{[42].} Another diabetic complication, ketoacidosis, increases stroke risk and is known to induce acute cerebral infarction\textsuperscript{[43-46].} Diabetic ketoacidosis causes systemic inflammation disrupting vascular endothelia structure and tight-junction function, coagulopathy, increased hemorrhagic and thrombotic risk and impaired cerebral autoregulation\textsuperscript{[45-48].} When diabetic ketoacidosis is complicated with hypertension and/or hyperlipidemia (commonly present in diabetic patients), stroke risk is further increased\textsuperscript{[43,44].} Diabetes induces pathologic neovascularization contributing to retinopathy, however diabetes can impair neovascularization and cause regression in other vascular beds like the brain\textsuperscript{[49].} Typically, angiogenic genes are unregulated with stroke shortly after the event as angiogenesis after stroke greatly improves functional recovery\textsuperscript{[50,51].} In diabetic condition after stroke, neangiogenesis is impaired but improved with more intensive glucose control and blood pressure control\textsuperscript{[52-56].} In conclusion, diabetes induces vascular changes that are conducive of stroke events and poorer stroke recovery.

**Glia cells**

Glia cells are the most abundant cell type in the brain; the three main types are astrocytes, oligodendrocytes and microglial cells. Although they do not directly participate in synaptic signaling they have important supportive functions like maintaining the necessary chemical environment for proper signaling, myelination of axons to assist axon potential conductance and mediating response to brain injury. As compared to the non-diabetic stroke model mice, the diabetic stroke model showed epigenetic down-regulation of connexin-43, GFAP and CD11b in glial cells\textsuperscript{[54].} Connexin-43 is a component of astrocyte gap-junction, essential for gap-junction structure and
function. In stroke, connexin-43 expression and translocation is disrupted and over-expression can stabilize astrocytes, rescue astrocytes from stroke's detrimental effect and promote neuronal recovery[65]. GFAP promotes axonal remodeling and motor behavioral recovery post stroke and is important in maintaining blood brain barrier properties and white matter vascularization[58-60]. This is consistent with reports that the blood brain barrier has compromised permeability under diabetic condition[61]. CD11b is a well-established proinflammatory cytotoxicity and phagocytosis marker[62]. In stroke condition it is usually up-regulated for microglial activation[63]. CD11b down-regulation in diabetic stroke is difficult to interpret without more spatiotemporality as targeted phagocytosis may assist in early synaptic remodeling and containment of injury[64]. Additionally, the role of microglial in stroke is complex in that microglial activation can result in a range of phenotypes both pro- and anti-inflammatory and phagocytosis can attenuate inflammation but also cause more neuronal damage by phagocytosis of viable neurons[65,66]. Therefore, the role of microglial in stroke in presence of diabetes needs to be further studied. Glutamate uptake by astrocytic glutamate transporters is important to maintain a low extracellular concentration to avoid excitotoxicity and neuronal damage. In the case of neuronal injury by stroke, glutamate is excitotoxified at great quantities causing excitotoxicity, ion imbalance and neuronal death. STZ-diabetic mice show no change in glutamate transporter (GLT-1 and GLAST) levels despite others reporting decrease in glutamate uptake in STZ-diabetic mice indicating a possible decrease in functionality of protein[67]. This suggests that although diabetes and prolonged hyperglycemia does not affect the number of glutamate transporter, it may be impairing transporter function. Diabetes also reduces oligodendrocyte progenitor cell proliferation and survival under chronic ischemia which both correlated with more severe white matter injury[68]. Diabetes results in more demyelination during stroke and less remyelination in the recovery of the ischemic penumbra[69]. In conclusion, the diabetic condition can impair glial function in turn compromising neuronal health and impair glial reaction to ischemic injury thereby exacerbating stroke injury.

**K<sub>ATP</sub> channels**

Potassium channels are ubiquitously expressed ion channels, present across essentially all cell types[70]. Opening of K<sup>+</sup> channel leads to an efflux of K<sup>+</sup> ions, hyperpolarizing the cell. Adenosine triphosphate (ATP)-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels conduct weak inward rectifier potassium current and belong to the Kir superfamily of K<sup>+</sup> channels. K<sub>ATP</sub> channels are composed of 4 pore-forming subunits (Kir6.1 or Kir6.2 encoded by KCNJ8 and KCNJ11, respectively) and 4 regulatory sulfonylurea receptor SUR ATP-binding cassettes subunits (subfamily C: SUR1, SUR2A or SUR2B). K<sub>ATP</sub> channels are inhibited by ATP and activated by Mg-ADP, allowing the cell to couple cellular metabolic state (ATP/ADP ratio) to electrical activity of the cell membrane. In pancreatic beta cells Kir6.2/SUR1 are the major subunits expressed, in cardiac myocytes Kir6.2/SUR2A subunits, in smooth muscles SUR2B, in adipose tissue Kir6.1/SUR2B, and in the brain neurons mostly Kir6.2/SUR1 while in astrocytes only Kir6.1/SUR1 and 2[71-75]. K<sub>ATP</sub> channels were first described in isolated ventricular myocytes of the guinea pig[76], and have been studied for their role in diseases from diabetes and hyperinsulinemia to cardiac arrhythmias and cardiovascular disease. K<sub>ATP</sub> channels mediate insulin secretion in pancreatic islet beta cells, and controlling vascular tone[77]. Under pathophysiological conditions, K<sub>ATP</sub> channels play cytoprotective role in cardiac myocytes and neurons during ischemia and/or hypoxia[78-81].

**Neuroprotective effect of K<sub>ATP</sub> channels in stroke**

In a stroke or an ischemic event, there is a shortage of oxygen and/or nutrient delivery and hence reduction of cellular ATP. Therefore, K<sub>ATP</sub> channels are activated by the rise in ADP/ATP ratio. This increase in K<sub>ATP</sub> channel activity and hyperpolarization during an ischemic event is thought to be important for protecting the cells from cell death and excitotoxicity[82,83]. In ischemic conditions, activation of K<sub>ATP</sub> channels underline many cardioprotective mechanisms[78]. Alphalipoic acid, diosgenin, estrogen, atorvastatin, vitamin C and angiotensin III have all been implicated as therapeutic agents for purpose of cardioprotection and suggested to function via K<sub>ATP</sub> channels[84-86]. Aside from these cytoprotective agents, K<sub>ATP</sub> channels are implicated in ischemic preconditioning in the heart[91]. Ischemic preconditioning is when one or several intermittent periods of ischemia disconcertingly results in protection against tissue damage by a subsequent and sustained ischemic injury[79]. K<sub>ATP</sub> channel activation prior to ischemic event mimics the effects of ischemic preconditioning[78,80,92]. Similarly, in the brain K<sub>ATP</sub> channels play a role in ischemic tolerance in stroke, conferring neuroprotection[93]. In diabetic brain, expression of Kir6.2 was significantly reduced, however, whether SUR1 expression was affected remained inconclusive[90].

**Neuronal K<sub>ATP</sub> channels**

K<sub>ATP</sub> pore forming subunits Kir6.1 and Kir6.2, as well as their regulatory subunits SUR1 and 2B, are expressed at high levels in the brain (cortical and hippocampal areas)[75,74,81,94,95]. Neuronal K<sub>ATP</sub> channels play an important role in regulating neuronal excitability and spontaneous firing in neurons including cholinergic basal forebrain neurons, excitatory neurons, entorhinal layer 3 cortical neurons, substantia nigra neurons, thalamocortical neurons[96-100]. Neuronal K<sub>ATP</sub> channels also play a critical role in glucose homeostasis at the hypothalamic level by regulating the secretion of glucagon and catecholamines[101]. In neuronal monocultures, pretreatment with diazoxide, a of K<sub>ATP</sub> channel opener, induced delayed preconditioning against oxygen glucose deprivation (OGD) and reduced cell death. These effects of diazoxide were suggested via inhibition of succinate dehydrogenase not mitochondrial K<sub>ATP</sub> channel[102]. Hippocampal neuron culture studies suggest that diazoxide decreases neuron apoptosis by preventing cytochrome c release, increasing Bcl-2 release and inhibiting Bax association.
with mitochondria\textsuperscript{[103]}. In a study comparing $K_{ATP}$ channel blocker and activator, blocker increased neuronal death in OGD of cultures while activator conferred neuroprotection\textsuperscript{[104]}. Activation of $K_{ATP}$ channels is neuroprotective in both focal and global ischemia \textit{in vivo} models, and the in vitro results suggest these effects are mediated at least in part by neuronal $K_{ATP}$ channels\textsuperscript{[81,94,95,105]}.

**Glial $K_{ATP}$ channels**

Astrocytes can provide protection in the event of ischemic events by supporting blood brain barrier integrity, reducing glutamate excitotoxicity and donation of mitochondria to neurons during recovery\textsuperscript{[106]}. Glutamate uptake by astrocytic glutamate transporters maintains low extracellular concentration to avoid excitotoxicity. Selective activation of mitochondrial $K_{ATP}$ channels in astrocytes increases glutamate uptake in culture which could confer an protective advantage\textsuperscript{[107]}. However, there has not been \textit{in vivo} confirmation of these findings. In astrocyte monolayers, the channel opener diazoxide pretreatment induced delayed preconditioning against oxygen glucose deprivation (OGD) blocking cell death as did in neuronal cultures suggesting that the protective effects observed \textit{in vivo} may be in part due to astrocytic $K_{ATP}$ channels\textsuperscript{[108]}. In primary microglia cultures, $K_{ATP}$ channel opener can prevent rotenone-induced microglia activation and neuroinflammation. In BV2 microglia cell line, the channel blocker glibenclamide increased reactive microglia, phagocytic capacity and TNFα release in response to pro-inflammatory signalling\textsuperscript{[109,110]}. Activated microglia at early phases of stroke was correlated with neuroprotection\textsuperscript{[110]}. Currently, it is not clear whether Kir6.x channel subunits are affected by diabetes, however hyperglycemia can reduce expression and function of astrocytic ATP-sensitive Kir4.1 channels in parallel with a decrease in glial glutamate level, suggesting a role of astrocytic potassium channels in poor stroke prognoses\textsuperscript{[111]}. Since diabetes induced S-glutathionylation of Kir6.1 is likely not limited to vasculature, the reduction of functional Kir6.1 subunit containing $K_{ATP}$ channels in diabetic condition could exacerbate ischemic stroke-induced brain damage. Astrocytes and oligodendrocytes ubiquitously express Kir6.1 and SUR1 which are activated under ischemic condition, however the specific function and/or expression of the glial channels in diabetes have not been thoroughly studied\textsuperscript{[112-114]}.

**Vascular $K_{ATP}$ channels**

$K_{ATP}$ channels are expressed in vascular smooth muscle\textsuperscript{[115,116]}, likely Kir6.1 and SUR2B subunits\textsuperscript{[117,119]}. Vasodilators (e.g. adenosine, calcitonin gene-related peptide and beta-agonists) and –constrictors (angiotensin II, endothelin-1 and vasopressin) increase or decrease $K_{ATP}$ channel activity, respectively, via PKC pathways\textsuperscript{[115,119-121]}. $K_{ATP}$ channels in the vasculature regulate vascular tone and blood flow to all organs including the brain. Vascular muscle $K_{ATP}$ channel activation causes vasodilation by controlling arterial diameter\textsuperscript{[122]}. In healthy volunteers glibenclamide (SUR class $K_{ATP}$ blocker) blocked while diazoxide ($K_{ATP}$ channel opener) mimicked endothelial ischemic preconditioning in humans\textsuperscript{[123]}. Before an ischemic event, $K_{ATP}$ mediated ischemic preconditioning of endothelial and during an ischemia event, vascular smooth muscle $K_{ATP}$ activation may be favourable as vasodilation could increase perfusion to the tissue and be therapeutic. In pathological conditions like hypertension (a stroke risk factor), the vasodilation response to $K_{ATP}$ channels is impaired at large cerebral arteries and microvessels (much like with $K_{ATP}$ channel blocker) and may predispose brain to ischemia and stroke\textsuperscript{[124]}. Therefore blockade of vascular $K_{ATP}$ channels can worsen hypertension and reduces blood flow which may predispose tissues to larger infarctions in the event of stroke\textsuperscript{[125]}.

### $K_{ATP}$ channels in \textit{in vivo} stroke models

Middle cerebral artery occlusion (MCAO) of rodents is a commonly used animal model for focal stroke. $K_{ATP}$ channel opener diazoxide reduced neuronal damage after MCAO\textsuperscript{[126]} and also induced delayed preconditioning against transient focal cerebral ischemia and reduced infarction volumes\textsuperscript{[127]} in rats. Similarly, activation of mitochondrial $K_{ATP}$ channels by BMS-191095 reduced total infarction volume in rats undergone MCAO\textsuperscript{[127]}. Consistent with these observations, $K_{ATP}$ channel blocker tolbutamide increased infarction volume and neurological deficits in MCAO model in mice, while $K_{ATP}$ channel opener provided neuroprotection\textsuperscript{[104]}. A separate study using 5-hydroxydecanoate as antagonist and diazoxide as agonist in MCAO rat model showed these effects were conserved\textsuperscript{[128]}. These findings were further confirmed in genetic knockout mouse model, indicating endogenous cortical $K_{ATP}$ channel activation provides protection against cerebral ischemic stroke induced infarction and neurological deficits\textsuperscript{[126,130]}. In transgenic mice overexpressing Kir6.2 channel, the animals exhibited strong neuroprotection against hypoxic-ischemic injury\textsuperscript{[131]}.

There are some conflicting accounts from studies using glibenclamide and glyburide, the second generation of sulfonylurea class $K_{ATP}$ channel blocker. Used alone or in combination with hypothermia, glibenclamide improved neurological outcome after MCAO in rats and 30 day survival were improved\textsuperscript{[132-134]}. SUR1 subunit can couple with non-selective cation channel, transient receptor potential melastin 4 (TRPM4) channel, which is involved in development of cerebral edema in brain injury\textsuperscript{[135-137]}. It is possible that glibenclamide affects the SUR1-TRPM4 complexes, thus reduced cerebral edema and swelling following stroke\textsuperscript{[138-141]}. Overall, animal studies suggest $K_{ATP}$ channel openers reduce and the channel blockers increase brain damage. Further studies are required to understand the
mechanisms underlying the differential effects of sulfonylurea class $K_{ATP}$ channel blockers on stroke severity.

There is abundant evidence that $K_{ATP}$ channel activity is neuroprotective in ischemic events. Not surprisingly, there are a plethora of patents involving $K_{ATP}$ channels and neuroprotection[142]. Activation of $K_{ATP}$ channels hyperpolarizes neurons, which can prevent excitotoxicity, stabilize membrane potential, reduce ionic imbalance and protect neurons from ischemia-induced death[129]. A schematic diagram is shown in Figure 1.

**Figure 1.** $K_{ATP}$ channels are neuroprotective and sulfonylurea use can exacerbate ischemia-induced brain damage. In the pancreatic β cells, $K_{ATP}$ channels serve as a metabolic sensor to post-prandial glucose metabolism. The closure of $K_{ATP}$ channels depolarizes cell membrane, activates voltage-gated calcium channels (VGCCs), and thus leads to insulin release. In the diabetic patients, sulfonylureas can be used to block $K_{ATP}$ channels and increase insulin release. In an ischemic neuron, the reduction in ATP:ADP ratio opens $K_{ATP}$ channels, lowering membrane potential and stabilizing the membrane, thus reducing cell excitotoxicity. In the diabetic patients using sulfonylureas, the neuroprotective effects of $K_{ATP}$ channels are abolished.

$K_{ATP}$ channel blockers in diabetes treatment

A prime example of $K_{ATP}$ channels coupling metabolism to electrical activity is in pancreatic beta cells. Glucose metabolism causes depolarization of the cell linking to insulin secretion. When glucose enters via GLUT2 transporter and it is metabolized by glucokinase resulting in increase in ATP/ADP ratio. ATP induces $K_{ATP}$ channel closure causing beta cell depolarization, voltage-gated calcium channel activation and leading to calcium-dependent insulin release (Figure 1). SUR subunit facilitates $K_{ATP}$ current via its ADP-binding. SUR1 paired potassium channel are highly sensitive to sulfonylurea inhibition and diazoxide activation[143]. In special circumstances, PIP2 can uncouple Kir6.2 from sulfonylurea bound SUR1, producing SU-independent current[23]. Mutations that alter $K_{ATP}$ channel activity are commonly seen in patients with neonatal diabetes, hyperinsulinemia and developmental delay-epilepsy-neonatal diabetes (DEND syndrome)[144-147]. Specifically, mutations in SUR subunit are associated with diabetes[148]. $K_{ATP}$ channels and SUR modulatory subunits act as key drug targets for diabetes hyperglycemic control. SUR subunit renders $K_{ATP}$ channels sensitive to sulfonylureas. Sulfonylureas, $K_{ATP}$ channel blockers, are the oldest class of hyperglycemic controlling drugs. Sulfonylureas reduce MgADP binding and efficacy of ADP-induced opening, and results in closure of $K_{ATP}$ channel[149]. Effectively, sulfonylureas block $K_{ATP}$ channel activity and induce insulin release (Figure 1).

$K_{ATP}$ channels are a major drug target in type 2 and neonatal diabetes. Closure of $K_{ATP}$ results in depolarization and insulin secretion in pancreatic β cells (Figure 1). SUR blockers can be categorized into two sets, drugs that block both SUR1 and SUR2: glibenclamide, glimepiride, repaglinide, meglitinide...
and those that are SUR1 specific: tolbutamide, nglilazide and nateglinde\cite{130}. Gliclazide and tolbutamide inhibition is readily reversible while glibenclamide, glimepiride and repaglinide exhibit a much slower reversibility. Glibenclamide binds to SUR1 at two sites, thus perhaps rendering slow dissociation. This is in line with the similar structure between glibenclamide and glimepiride\cite{130}. Sulfonylurea class anti-diabetic drugs and its derivatives are used in diabetes mellitus to stimulate insulin release and control blood glucose. Clinically, they are classified into three generations: the second and third generation sulfonylureas are generally safer (i.e. lower risk of hypoglycemia, cardiovascular events) than the first generation. Sulfonylureas have potent glucose lowering effects and newer oral antidiabetics (including metformin, thiazolidinediones, exenatides, and symlins) show lower risk of inducing hypoglycemia, thus are a popular choice in western-healthcare. However first generation of sulfonylureas remains the key in diabetes care in developing countries\cite{131,132}.

**Cerebrovascular safety of SUR blocking anti-diabetic drugs and future directions**

The American College of Physicians (ACP) in clinical practice guideline updates for oral pharmacological treatment of T2D states that sulfonylureas are associated with weight gain and more episodes of hypoglycemia than metformin\cite{133}. However, there is low quality and inconsistent evidence to suggest sulfonylureas alone or metformin combination treatment increases cardiovascular risks/all-cause mortality as compared to metformin treatment of T2D. A recent meta-analysis of sulfonylurea treatment of diabetes and stroke risk summarizes 17 randomized controlled trials concluded with high confidence that sulfonylureas monotherapy or combination therapy increases the number of stroke events in diabetic patients as compared to comparator drug or placebo group\cite{104,154}. Since then there have been other reviews on cardiovascular events and anti-diabetic agents, however no new analysis focusing on stroke and sulfonylureas\cite{155-159}. In line with the ACP, other independent reviews including Cochrane review of 301 clinical trials conclude that sulfonylurea safety in treatment of diabetes is still unclear\cite{137,138,160}. As for stroke risk, studies of effects of sulfonylureas on stroke severity and recovery are incomplete\cite{161-164}. Despite new evidences emerging, due to many conflicting accounts in both animal and human studies, cerebrovascular safety of sulfonylurea remains controversial\cite{161,163,165-168}.

Many sources could contribute to the heterogeneity among the studies. For instance, the wide variety of sulfonylureas has been used in studies or prescribed in clinics (different generations, short, intermediate or long acting). Clinical/epidemiological studies that indicate the specific sulfonylurea subgroup analysis are insufficient. Sulfonylurea subgroup analysis by generation has been employed in terms of evaluating risk of hypoglycemia however cardiovascular and cerebrovascular risk are newer areas in comparison\cite{149}. Although there has been no report comparing the types of sulfonylurea, one meta-analysis that excluded studies using first generation sulfonylureas found no appreciable increase in all-cause mortality, stroke or myocardial infarction with prescribed second or third generation sulfonylureas\cite{148}. To move forward, new studies in relationship between sulfonylurea use and cerebrovascular mortality, as well as all-cause mortality should specify individual sulfonylureas used by each participant.

Sulfonylureas target a fundamental step of insulin secretion and are effective in treating diabetes with diverse genetic causes, thus are useful where genetic testing is not readily available\cite{170}. The heterogeneity of their effects on stroke might be in part related to genetic polymorphisms at the cytochrome P450 2C9 (CYP2C9) gene, encoding the enzyme that primarily metabolizes sulfonylureas\cite{171} or at the ABCC gene sites. Individual differences affecting how the body processes sulfonylureas to how the sulfonylureas act on the targets remained to have a large impact. In line with these possibilities, efforts could be made in pharmacogenetics to determine patients with CYP2C9 mutations (CYP2C9*3/*3) which prolong effects of sulfonylureas in the body\cite{172}. This poses a great challenge as the areas that have fast growing diabetic populations and tend toward sulfonylureas are unlikely to have access to genetic screening before treatment. In developing countries with limited access to genetic testing and limited resources, affordable and reliable treatments like sulfonylureas are highly valuable. According to the Association of Physicians of India, sulfonylureas are prescribed as their first line for non-obese diabetic patients by most of doctors\cite{172}. Given the role of K\textsubscript{ATP} channels in neuroprotection, there is a concern for the safety of sulfonylureas usage in this population with increased risk of stroke.

The pharmacokinetic and pharmacodynamic profiles of each sulfonylureas are different. Prescribing sulfonylureas with lower permeability to the brain or shorter half-life could mitigate their effects on stroke risk while achieving insulin and glycemic targets. Further, sulfonylureas display almost complete serum protein binding (90%–99%) once absorbed and their clearance is hindered by renal impairment which is common in diabetics. Only tolbutamide has been studied for its ability to across the blood-brain-barrier and have a minimal serum accumulation\cite{173,174}. Under diabetic or stroke conditions, the blood-brain-barrier integrity is damaged and its permeability to drugs is altered\cite{175}, and thus detailed understanding of the levels of individual sulfonylureas in brain under these pathological/pathophysiological conditions should be further explored.

**Conclusion**

K\textsubscript{ATP} channels play important roles both in physiologic and pathophysiologic settings, from insulin secretion to cyto/neuroprotection. Activation of K\textsubscript{ATP} channels in ischemia and/or hypoxia can provide neuroprotection to stroke and hypoxia. Diabetes is one of the major risk factors for stroke and leads to more severe stroke outcomes particularly if hyperglycemic management is inadequate. Sulfonylurea class of antidiabetic drugs blocks K\textsubscript{ATP} channels which are neuroprotective in stroke, and can be one of the high stoke risk factors for diabetic patients. The first generation of sulfonylurea is currently
less used in clinics because of their potential side effects, however remains the first line of diabetic treatment in third world countries. Further studies are needed to verify whether the long term use of the K<sub>ATP</sub> channel blockers would increase the vulnerability of the brain to ischemic/hypoxic insult. As the incidence of diabetes increases, to fully and safely capitalize on sulfonylureas, focus could be made on finding effective ways to stratify the population into well-defined risk groups so that sulfonylureas can be used safely. Until the risks are clear, the data warrant caution when recommending sulfonylurea as treatment especially if patients display high risk for stroke.

Acknowledgements
VYS holds an NSERC Canada Graduate Scholarship. This work was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) Discovery Grants, to Zhong-ping FENG (RGPIN-2014-06471) and to Hong-shuo SUN (RGPIN-2016-04574).

Abbreviation
K<sub>ATP</sub> channel, adenosine triphosphate-sensitive K<sup>+</sup> channel; ABCC, ATP-binding cassette transporter sub-family C; KCNJ, Potassium Voltage-Gated Channel Subfamily J; Kir, Inward-rectifier potassium channel; OGD, oxygen-glucose deprivation; SUR, sulfonylurea receptor; rtPA, recombinant tissue plasminogen activator; TRPM4, transient receptor potential melastatin 4; GLUT2, glucose transporter 2; VGCC, voltage-gated calcium channel; MCAO, middle cerebral artery occlusion; GFAP, glial fibrillary acidic protein; ROS, reactive oxygen species; STZ, streptozotocin; GLUT2, glucose transporter 2; GLAST, glutamate aspartate transporter; ACP, American College of Physicians; CYP2C9, cytochrome P450 2C9.

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