Review Article

Sulfonylurea and neuroprotection: The bright side of the moon

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Abstract

Sulfonylurea (SUR) agents are the second and most used oral hypoglycemic drugs after metformin and they still as an imperative tool for most favorable of glucose control. SURs are used mainly in the management of Type 2 diabetes mellitus since; they are effective in the glycemic control and reduction of microvascular complications. First-generation SUR represents 3% of used oral hypoglycemic agents while second and third generations are used in about 25% in patients with Type 2 diabetes mellitus. Upregulation of SUR1 receptor has been observed after stroke and traumatic brain injury, therefore, SUR such as glibenclamide inhibits brain edema and astrocyte swelling following brain insults. SUR drugs mainly glibenclamide is effective at a low dose in the management of cerebral stroke and could be a contestant with corticosteroid in controlling brain edema.

Key words: Sulfonylurea, stroke, type 2 diabetes mellitus

INTRODUCTION

Sulfonylurea (SUR) agents are the second and most used oral hypoglycemic drugs after metformin, and they still as an imperative tool for most favorable of glucose control. SUR drugs have pancreatic and extra-pancreatic effects in the regulation of blood glucose through stimulation the release of insulin from pancreatic β-cells, inhibition of glucagon release, and reduction of hepatic insulin clearance.[1] Uses of SUR drugs have much pros and cons in the clinical practice such as weight gains, hypoglycemia, and cardiovascular outcomes; thus, their safety and clinical benefit have been a matter of debate.[2]

SUR is used mainly in the management of Type 2 diabetes mellitus since; they are effective in the glycemic control and reduction of microvascular complications. The first-generation SUR represents 3% of used oral hypoglycemic agents while second and third generations are used in about 25% in patients with Type 2 diabetes mellitus.[3,4]

SUR receptors are the molecular target of SUR drugs; there are three types of these receptors which are SUR1, SUR2A, and SUR2B.[5]

The main function of these receptors is to sense the intracellular levels of adenosine triphosphate (ATP) and adenosine diphosphate in response to the potassium channels, thus, K_{ATP} channel and nonselective cation channel (NCCa-ATP) observes and sense the intracellular energy balance.[6]

High glucose levels increase the production of ATP which triggers the closure of K_{ATP} channel causing change in the pancreatic β-cell membrane potential that activates the opening of ca-channel leading to insulin exocytosis.[7]

Upregulation of SUR1 receptor has been observed after stroke and traumatic brain injury in rats, therefore, SUR

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drugs such as glibenclamide inhibits brain edema and astrocyte swelling following brain insults.[8]

Moreover, animal modeled study illustrated an over-expression of SUR1 receptor in ammonia cultured astrocyte and the cortical neurons after induced hepatic encephalopathy while treatment with glibenclamide reveres these pathological changes, these findings proposed the neuroprotective effect of SUR.[9]

Glibenclamide produces dose-independent reduction in brain edema induced by neuronal damage since; glibenclamide at a dose of 2 mg/kg or 5 mg/kg illustrated insignificant differences on brain edema in rats due to inhibition of neuronal-specific K-Cl cotransporter.[10]

Cerebral ischemia activates the release of hypoxia-inducible factor 1/2 which plays a crucial role in up-regulation of SUR1 receptor,[11] also neuronal damage induced by cerebral ischemia provokes the stimulation of protein and mitogen-activated protein kinases which are involved in the acceleration of SUR1 receptor currents and subsequent K_{ATP} and NCCa-ATP channels.[12]

Moreover, Kurland *et al.*, study illustrated that SUR1 receptors are linked with transient receptor potential melastatin 4(Trpm4) which plays an important role in the progression of brain edema, damage of blood–brain barriers and neuronal death. Up-regulated Trpm4 protein remains about 1 month after cerebral infarction; therefore, a pharmacological inhibition of these channels by SUR drugs may reduce the complications of cerebral infarction.[13]

Normally, SUR drugs such as glibenclamide not accumulated in the neurons under normal physiological condition but during stroke, penetration of SUR drugs are enhanced due to breakdown of blood–brain barrier and neuronal acidic PH as well as selective trapping of SUR drugs in the ischemic areas, thus glibenclamide is mainly accumulated in the injured but not in the normal neurons.[14]

Recently, glibenclamide has a new attention due to its pleiotropic effects; it inhibits Sur1-regulated NCCa-ATP channel leading to anti-inflammatory effects and activation of neurogenesis which *per se* ameliorate cerebral stroke, spinal cord injury, premature encephalopathy, and traumatic brain injury.[15]

Therefore, glibenclamide intravenous formulation has been developed for the management of acute brain injury since; uses of glibenclamide in this context are highly promising due to the improvement of stroke outcomes in many animal model studies.[16,17]

In addition, recombinant tissue plasminogen activator which is approved by FDA for ischemic stroke is associated with risk of bleeding due to activation of matrix metalloproteinase 9 (MMP9). Glibenclamide inhibits MMP9 activation, therefore, a combination of glibenclamide with tissue plasminogen activator improves stroke outcomes.[18]

The neuroprotective effect of glibenclamide may be beyond SUR1 blocking effect as supported by Ortega *et al.*, study that demonstrated a potential blocking effect of glibenclamide on microglial K_{ATP} channel leading to augmentation of microglia phagocytic activity with modulation of proinflammatory cytokines release and then reduction of neuronal loss and necrosis.[19]

Preclinical study by Simard *et al.*, disclosed that glibenclamide improves stroke score and outcomes after ischemic stroke with significant amelioration in the cognitive and sensory-motor performances due to activation of cortical and hippocampal angiogenesis.[20]

In this context, most of the previous and current studies focused on the glibenclamide as a prototype SUR drug, but recent meta-analysis study confirmed that second and third generations SUR are safe and effective neuroprotective agents as glibenclamide in attenuation of cerebral stroke complications.[21]

Recently, Douros *et al.*, study illustrated differences in the cardiometabolic and risk of neurological complications from different SUR drugs, short-acting SUR such as gliclazide and glipizide are associated with a high risk of stroke while long-acting such as glimepiride and glibenclamide reduce the risk of stroke and neurological complications.[22]

On the other hand, Monami *et al.* observational study reported that the uses of SURs are associated with an increase in the cardiovascular complications and stroke risk due to interfering with cardiac ATP-sensitive k-channels leading to cardiac dysfunction and arrhythmias.[23]

As well, a systematic meta-analysis study done by Liu *et al.* disclosed that diabetic patients treated with SUR are at high risk of stroke compared to the other oral hypoglycemic drugs.[24]

It has been mentioned by many researchers the link between SUR and other cardio-metabolic complications which might be falsely positive or negative conclusions since; these contradictory studies explained by short-term or observational studies.[25]

Recently, King *et al.*, human study confirmed the potential role of glyburide in blocking SUR1-TRPM4 which are concerned with the development of brain edema and microvascular dysfunction in patients with extensive hemispheric stroke.[26]

A recent study disclosed that therapeutic hypothermia is efficient models of therapy in the prevention of brain edema and mortality rate during experimental cerebral stroke in rats. Glibenclamide potentiates and produced synergistic effect with therapeutic hypothermia in the prevention of stroke complications through inhibition of stroke-induced cytokine releases.[27]

Previously, Darsalia *et al.* disclosed that glimepiride was effective in stroke prevention in normal but not in diabetic mice through augmentation of insulin levels which has a neuroprotective effect, therefore, this drug is ineffective in prevention of stroke initiation and complications compared to linagliptin drug.[28]

Thus, the estimation of individual drug of SUR group is recommended to clarify the molecular differences at neuronal activity.

Therefore, from previous and extensive studies, SUR drugs mainly glibenclamide is effective at a low dose in the management of cerebral strokes and could be a contestant with corticosteroid in controlling brain edema.

CONCLUSION

SUR is effective in the management of cerebral strokes and could be a contestant with corticosteroid in controlling brain edema.

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Conflicts of interest
There are no conflicts of interest.

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