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Is There Enhanced Risk of Cerebral Ischemic Stroke by Sulfonylureas in Type 2 Diabetes?

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Hyperglycemia enhances stroke injury in humans and experimental animals, and type 2 diabetes mellitus (T2DM) is a known risk factor for stroke. Sulfonylurea (SU) drugs have been used for over six decades for management of T2DM; they exhibit their principal antidiabetes property by inhibiting K_{ATP} channels and promoting an increase in insulin secretion by pancreatic β-cells (1,2) (Fig. 1*A*). The K_{ATP} channel in the pancreas is a complex of four subunits of the KCNJ11 gene product Kir6.2 and four subunits of the ABCC8 gene product SUR1 (3). SU drugs bind to SUR1 to block the K_{ATP} channel.

Although treatment of T2DM reduces stroke risk, the study by Liu et al. (4) in this issue of *Diabetes* addresses the question of whether SU drugs can enhance stroke risk and stroke injury by inhibiting K_{ATP} channels in brain. The study makes three points. First, a 5-day administration of streptozotocin (STZ) to mice led to persistent hyperglycemia (blood glucose >16 mmol/L) and decreased body weight (<10% from controls); following a 90-min transient middle cerebral artery occlusion (MCAO), infarct size and neurological deficit were both significantly greater in mice given STZ. Second, in cortical mouse neurons subjected to oxygen-glucose deprivation and in normoglycemic mice subjected to permanent MCAO, neuronal cell death and stroke injury were increased with the SU tolbutamide but decreased with the K_{ATP} channel opener diazoxide. Third, a meta-analysis of human clinical trials in patients with T2DM was performed. Seventeen randomized controlled trials, with a combined total of over 27,000 patients, that compared SUs to placebo or other antidiabetes drugs and reported stroke incidence were included. The analysis revealed a >30% increase in the incidence of stroke in patients treated with SUs. Thus, this report concludes that SU drugs increase stroke risk and are used in a patient population that is already at greater risk of stroke (4).

The study by Liu et al. supports the findings of a previous study by the senior authors, which reported increased stroke injury using transient MCAO in Kir6.2 knockout mice relative to wild-type mice (5). However, there are other reports describing beneficial effects of SU drugs in rodent models of cerebral ischemia (6–8). Interestingly, in the brain, SUR1 serves as a regulatory subunit for both the K_{ATP} channel and a nonselective cation channel, $NC_{Ca\text{-}ATP}$ (9). The pore-forming subunit of the $NC_{Ca\text{-}ATP}$ channel was recently identified as Trpm4 (10). The $NC_{Ca\text{-}ATP}$ channel conducts monovalent cations, is activated by depletion of cellular ATP, and requires nanomolar concentrations of Ca^{2+} for opening (11). Thus, ischemic conditions are reported to trigger opening of both K_{ATP} and $NC_{Ca\text{-}ATP}$ channels, but whereas K_{ATP} channel opening is hyperpolarizing, $NC_{Ca\text{-}ATP}$ channel opening is depolarizing (Fig. 1*B*). In rodent models of cerebral stroke, it was demonstrated that blockage of newly expressed SUR1 in ischemic neurons, astrocytes, and capillaries with a low dose of the SU glibenclamide reduced cerebral edema, infarct volume, and mortality by 50%, and this was associated with cortical sparing (8). Simard et al. (8) hypothesized that the $NC_{Ca\text{-}ATP}$ channel is crucially involved in development of cerebral edema and that targeting SUR1 may provide a new therapeutic approach to stroke. Another study reported beneficial effects of glibenclamide in a rat global forebrain ischemia-reperfusion model; antioxidant and anti-inflammatory effects, rather than K_{ATP} or $NC_{Ca\text{-}ATP}$ channel activities, were observed (6).

Resolving these differences should provide important information for the basic science of stroke pathology, stroke treatment, and the pharmacology of SU drugs. In principle, the beneficial/detrimental effects of individual SU drugs could be due to *1*) differing affinities for SUR1 in association with Kir6.2 versus Trpm4, *2*) differing affinities for non-SUR1 targets, *3*) differing blood-brain barrier permeability or drug trapping within ischemic brain tissue, and/or *4*) differences between stroke models and animal species among research laboratories.

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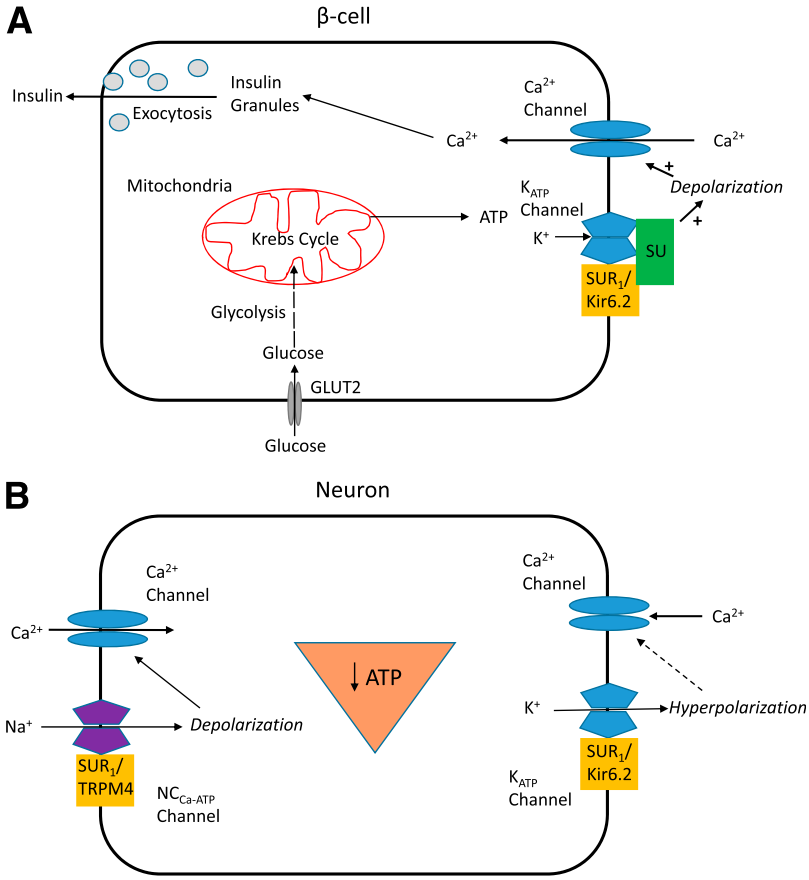

Figure 1—Intracellular depletion of ATP triggers opening of K_{ATP} and $NC_{Ca\text{-}ATP}$ channels. *A*: Increase in circulating glucose results in rapid glucose movement into pancreatic β-cells through the GLUT2 glucose transporter. The cytosolic glucose is converted by glycolysis to pyruvate, ATP, and NADH. The pyruvate and NADH is converted to ATP via the Krebs cycle in mitochondria. This ATP results in closure of the K_{ATP} channels, which results in membrane depolarization and activation of voltage-dependent Ca^{2+} channels. The influx of Ca^{2+} results in Ca^{2+}-dependent insulin granule secretion. The K_{ATP} channel is composed of Kir6.2 and SUR1 subunits. SU drugs bind SUR1 and inhibit channel opening to promote insulin secretion. *B*: While opening of K_{ATP} channels and K^+ efflux produces hyperpolarization and inhibits Ca^{2+} channel activity, opening of $NC_{Ca\text{-}ATP}$ channels and Na^+ influx produces depolarization and Ca^{2+} channel opening. SU drugs block both channels. In addition to being in neurons, $NC_{Ca\text{-}ATP}$ channels are also found in astrocytes, oligodendrocytes, and endothelial cells following an ischemic event (7). Solid arrow, stimulatory; dashed arrow, inhibitory.

Given that both beneficial and detrimental effects of SU drugs are observed in experimental stroke models, the question of the cerebrovascular safety of SU therapy for patients with T2DM and whether there is reduced or enhanced risk of ischemic stroke in these patients becomes even more important. This question has been addressed in several clinical studies of T2DM patients hospitalized with acute stroke and preadmission treatment with SU or other antidiabetes drugs. Interestingly, some studies report a potential benefit of SUs (12,13), whereas others report no benefit (14) or a potential detrimental effect (15). Given these mixed findings, as well as those of other reports not cited here, the meta-analysis performed by Liu et al. (4) is an important contribution. Their analysis has led to the conclusion that SU treatment may contribute a significant risk for stroke in this patient population.

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