Sulfonylurea receptor 1

Glibenclamide, also known as glyburide, is an antidiabetic drug in a class of medications known as sulfonylureas, closely related to sulfonamide antibiotics. It was developed in 1966 in a cooperative study between Boehringer Mannheim (now part of Roche) and Hoechst (now part of Sanofi-Aventis).

This second-generation sulfonylurea drug inhibits sulfonylurea receptor 1 (Sur1) at nanomolar concentrations.

Glibenclamide is a second-generation drug from the sulfonylurea family, which acts by inhibiting the adenosine triphosphate (ATP)-sensitive K channel in the regulatory subunit of type 1 sulfonylurea receptor (SUR-1) in pancreatic β cells. Glibenclamide reduces neuroinflammation and associated BBB injury by inhibiting the nod-like receptor pyrin 3 (NLRP3) inflammasome, oxidative stress, and microglial activation. Therefore, glibenclamide through inhibition of NLRP3 inflammasome, microglial activation, and oxidative stress may attenuate SARS-CoV-2-mediated neuroinflammation [1)].

It was repurposed to target Sur1-transient receptor potential melastatin 4 (Trpm4) channels in acute central nervous system injury. Discovered nearly two decades ago, SUR1-TRPM4 has emerged as a critical target in stroke, specifically in large hemispheric infarction, which is characterized by edema formation and life-threatening brain swelling. Following ischemia, SUR1-TRPM4 channels are transcriptionally upregulated in all cells of the neurovascular unit, including neurons, astrocytes, microglia, oligodendrocytes and microvascular endothelial cells. Work by several independent laboratories has linked SUR1-TRPM4 to edema formation, with blockade by glyburide reducing brain swelling and death in preclinical models. Recent work showed that, following ischemia, SUR1-TRPM4 co-assembles with aquaporin-4 to mediate cellular swelling of astrocytes, which contributes to brain swelling. Additionally, recent work linked SUR1-TRPM4 to secretion of matrix metalloproteinase-9 (MMP-9) induced by recombinant tissue plasminogen activator in activated brain endothelial cells, with blockade of SUR1-TRPM4 by glyburide reducing MMP-9 and hemorrhagic transformation in preclinical models with recombinant tissue plasminogen activator. The recently completed GAMES (Glyburide Advantage in Malignant Edema and Stroke) clinical trials on patients with large hemispheric infarctions treated with intravenous glyburide (RP-1127) revealed promising findings with regard to brain swelling (midline shift), MMP-9, functional outcomes and mortality. Here, we review key elements of the basic science, preclinical experiments and clinical studies, both retrospective and prospective, on glyburide in focal cerebral ischemia and stroke [2)].

In severe traumatic brain injury (TBI), contusions often are worsened by contusion expansion, or “hemorrhagic progression of contusion” (HPC), which may double the original contusion volume and worsen outcome. In humans and rodents with contusion-TBI, sulfonylurea receptor 1 (SUR1) is upregulated in microvessels and astrocytes, and in rodent models, blockade of SUR1 with glibenclamide reduces HPC. SUR1 does not function by itself, but must co-assemble with either KIR6.2 or TRPM4 to form KATP (SUR1-KIR6.2) or SUR1-TRPM4 channels, with the two having opposite effects on membrane potential. Both KIR6.2 and TRPM4 are reportedly upregulated in TBI, especially in astrocytes, but the identity and function of SUR1-regulated channels post-TBI is unknown. Here, we

analyzed human and rat brain tissues after contusion-TBI to characterize SUR1, TRPM4 and KIR6.2 expression and, in the rat model, to examine the effects on HPC of inhibiting expression of the three subunits using intravenous antisense oligodeoxynucleotides (AS-ODN). GFAP immunoreactivity was used to operationally define core versus penumbral tissues. In humans and rats, GFAP-negative core tissues contained microvessels that expressed SUR1 and TRPM4, whereas GFAP-positive penumbral tissues contained astrocytes that expressed all three subunits. Förster resonance energy transfer imaging demonstrated SUR1-TRPM4 heteromers in endothelium, and SUR1-TRPM4 and SUR1-KIR6.2 heteromers in astrocytes. In rats, glibenclamide as well as AS-ODN targeting SUR1 and TRPM4, but not KIR6.2, reduced HPC at 24 hours post-TBI. Our findings demonstrate upregulation of SUR1-TRPM4 and KATP after contusion-TBI, identify SUR1-TRPM4 as the primary molecular mechanism that accounts for HPC, and indicate that SUR1-TRPM4 is a crucial target of glibenclamide [3].

1)
Batiha GE, Al-Kuraishy HM, Al-Gareeb AI, Alruwaili M, AlRuwaili R, Albogami SM, Alorabi M, Saad HM, Simal-Gandara J. Targeting of neuroinflammation by glibenclamide in Covid-19: old weapon from arsenal. Inflammopharmacology. 2022 Nov 23:1–7. doi: 10.1007/s10787-022-01087-8. Epub ahead of print. PMID: 36418600; PMCID: PMC9685016.
2)
King ZA, Sheth KN, Kimberly WT, Simard JM. Profile of intravenous glyburide for the prevention of cerebral edema following large hemispheric infarction: evidence to date. Drug Des Devel Ther. 2018 Aug 15;12:2539-2552. doi: 10.2147/DDDT.S150043. eCollection 2018. Review. PubMed PMID: 30147301; PubMed Central PMCID: PMC6101021.
3)
Gerzanich V, Stokum J, Ivanova S, Woo SK, Tsymbalyuk O, Sharma A, Akkentli F, Imran Z, Aarabi B, Sahuquillo J, Simard JM M.D., Ph.D. SUR1, TRPM4 and KIR6.2 - role in hemorrhagic progression of contusion. J Neurotrauma. 2018 Aug 30. doi: 10.1089/neu.2018.5986. [Epub ahead of print] PubMed PMID: 30160201.