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LOWER CARDIAC RISKS ASSOCIATED WITH K-GLIM (GLIMEPIRIDE)

A sulphonylurea with low affinity for cardiac KATP channel

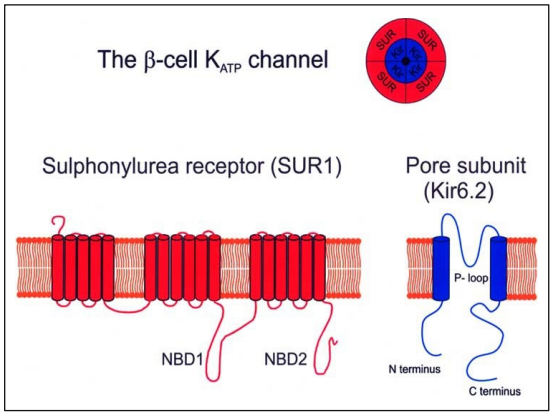
Despite the availability of newer types of anti-diabetic medications, sulfonylureas (SUs) remain one of the most frequently prescribed classes of non-insulin antihyperglycemic agents, primarily owing to their established glucose lowering efficacy, long experience of clinical use and low cost. SUs exerts its glucose lowering effect by primarily targeting adenosine triphosphate potassium-sensitive (KATP) channel for insulin secretion.

The β-cell KATP Channel Structure and Function

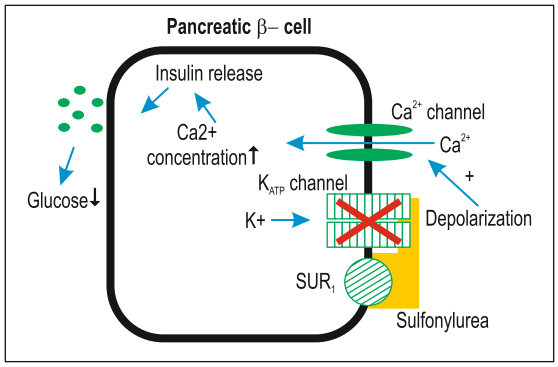
KATP channels are widely expressed in nearly all the tissues & is particularly important in the regulation of insulin secretion from pancreatic β–cells.

There are three isoforms of the Sulfonylureas receptor (SUR):

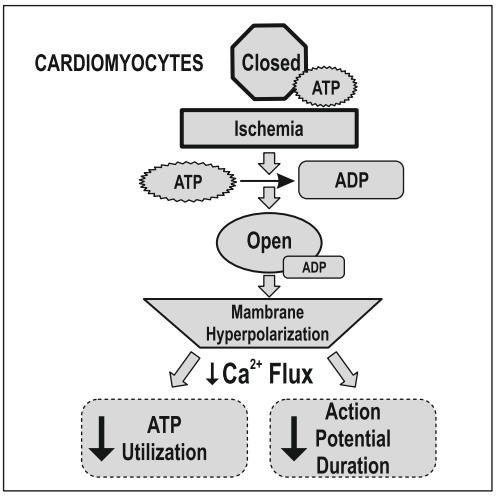
- SUR1 expressed in pancreas and neurons
- SUR2A in skeletal and cardiac muscle
- SUR2B, in smooth muscle and brain.



The KATP Channel and insulin secretion



KATP channel in the pancreas are usually in the open conformation under normal conditions. In pancreatic β–cells, high levels of ATP, corresponding to increased plasma glucose levels, result in KATP channel closure & Ca^{+2} influx leading to insulin release. SUs bind to the SUR1 subunit, inhibit KATP channel activity, potentiating Ca^{+2} influx & insulin release.



KATP Channels and Cardioprotection

Myocardial KATP channels are closed under normal physiological conditions. However, these channels open at the time of a metabolic insult, reducing cardiac excitability & protecting the myocardium against damage. This occurs due to decreased Ca^{+2} flux thereby reducing the contractions & consumption of cellular ATP. Thus, Cardiac mitochondrial KATP channel play a key role in cardio protection & since SUs target both pancreatic & cardiac mito KATP channels, they may interfere with the cellular pathway that confers cardio protection.

Pharmacotherapeutic Agents that Regulate KATP Channels

KATP channels are targets of many different pharmacological compounds & the best known drugs that regulate KATP channels are the sulfonylureas. Cardiovascular side effects do not seem to be uniform among all SUs due to their varying degree of affinity for the mito KATP channels.

- KATP channels possess both *high affinity* and *low affinity* binding sites for SUs. *Glyburide and Glipizide* have high affinity for cardiac mito KATP channel.
- *Glimepiride,* on the contrary, has a high affinity for β-cell Kir6.2/SUR1 KATP channel, but only a very low affinity for cardiac Ki6.2/SUR2A KATP channel.

Thus SUs with high affinity for mito KATP channels such as Glyburide and Glipizide are associated with an increased risk of major adverse cardio vascular events (MACE) in patients with T2DM as compared to SUs with low affinity such as Glimepiride.

The Clinical Evidence

A recent clinical study have reaffirmed the above hypothesis, in which T2DM patients treated with metformin plus SU (Glyburide/Glipizide), had a significantly increased risk of MACE (18% higher), all-cause mortality and severe hypoglycemia as compared to Glimepiride.

Support for the cardiovascular safety of glimepiride is strengthened by the results of *CARMELINA & CAROLINA* studies where it has been compared with Linagliptin.

Glimepiride was found to have lower risks of MACEs and hypoglycemia, it can be the preferred SU over other agents of the same class for the treatment of T2DM. This recommendation about the choice of sulfonylureas is of great clinical importance, given that sulfonylureas are one of the most used anti-diabetic drugs after metformin in current clinical settings, despite the presence of newer anti-diabetic medications.

Source: Wang MT, et al. JAMA Network Open. 2022;5 (12):e2245854; Riddle M et.al, Diabetes Care 2019;42(12):2161–2163;Wet HD, et al.Biochem. Soc. Trans. (2015) 43, 901–907;Burke MA, et al. Circulation research. 2008; 102(2): 164-176; Sato T, et al. Diabetes Metab Res Rev 2006; 22: 341–347.

ANGICAM (AMLODIPINE) THERAPY FOR COGNITIVE FUNCTION IMPROVEMENT

Role in Cerebrovascular disease

Alzheimer's disease (AD) is the leading cause of dementia, followed by vascular dementia (VaD) & affects 7% of people over 65 years. Disturbance of the intracellular calcium homeostasis is central to the pathophysiology of neurodegeneration.

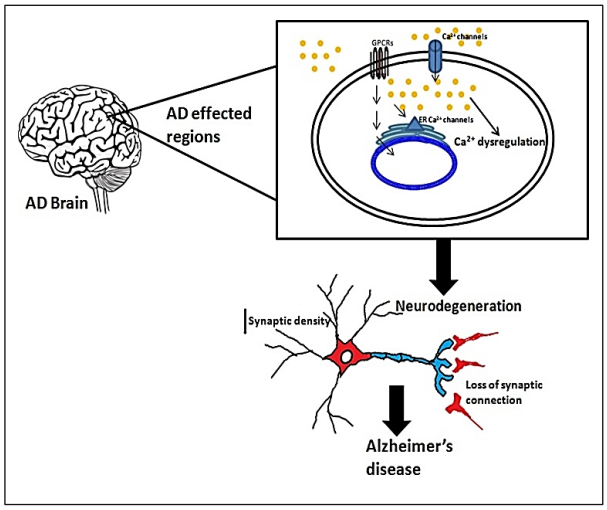
- AD is characterized by three neuropathological hallmarks: extracellular aggregates of amyloid-(Aβ) peptide (amyloid plaques), neurofibrillary tangles and synaptic loss.
- VaD is caused by either macroangiopathic or microangiopathic changes.

Need for newer therapy

Currently, two classes of medications approved for AD [cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) antagonist] show clinical benefit in some patients, however, many do not respond. Additionally, these drugs do not significantly modify disease progression and more importantly are not approved for patients at earlier stages of the disease (mild cognitive impairment; MCI). None to date have been proven useful in the modulation of the pathogenesis of AD and the cognitive decline associated with disease progression.

For these reasons there is a critical need to identify additional therapeutics that can be initiated early in disease progression to alter the pathogenesis of the disease.

Calcium signaling, excitotoxicity and AD



Calcium is a key intracellular messenger that mediates electrical and chemical stimulation responses. Maintenance of the intracellular calcium homoeostasis is fundamental to neuronal viability and functioning. During aging, the control of the intracellular calcium concentration is impaired, leading to neuronal dysfunction.

In AD, Aβ induces influx of extracellular calcium and clinical mutations in the presenilin gene further lead to calcium release from the endoplasmic reticulum which may lead to cell death.

At presynaptic terminals, voltage-gated calcium channels (VGCCs) mediate the release of neurotransmitter upon arrival of action potentials. A release of glutamate at central synapses facilitates calcium entry at postsynaptic sites through NMDA receptors and indirectly through L-type calcium channels. Excessive glutamate release leads to an imbalance of the postsynaptic calcium load, triggering intracellular cascades that finally cause neuronal death. This process, termed 'excitotoxicity', has been proposed to underlie the pathology of AD. Excitotoxicity can be attenuated by blocking calcium influx in both synaptic terminals as well as postsynaptic sites.

Besides, VaD, which makes up 25% of dementia cases, is caused by cerebral hypoperfusion and may benefit from the calcium channel blockade, which could improve cerebrovascular perfusion and relaxation of the cerebral vasculature.

Treatment with CCBs for improvement in cognitive decline: Clinical Evidences

Clinical evidences which corroborates the above hypothesis on usefulness of CCBs for cognitive function improvement:

- In a large European study, long-term hypertension therapy, especially with calcium antagonists, helped prevent VaD and AD.
- In a community based randomized clinical trial, long-term hypertension therapy with CCBs reduced the risk of dementia by 38–55% and correlated with cognitive function.
- A meta-analysis with CCBs identified a significant reduction in the risk of dementia in patients with CCB therapy compared to those without it.

Role of Amlodipine

- A recent study on 545 patients showed that 24 weeks of treatment with 5 mg S-amlodipine besilate was effective for improving Mini-Mental State Examination (MMSE) and Global Deterioration Scale (GDS) scores in patients with hypertension and cerebrovascular disease, regardless of whether the subject has reached the target blood pressure.

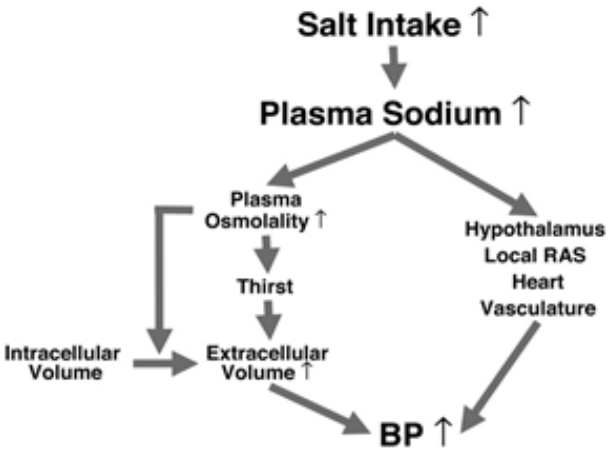
"Collectively, these data suggest the use of CCBs (Amlodipine) for cognitive function improvement in patients with cerebrovascular disease".

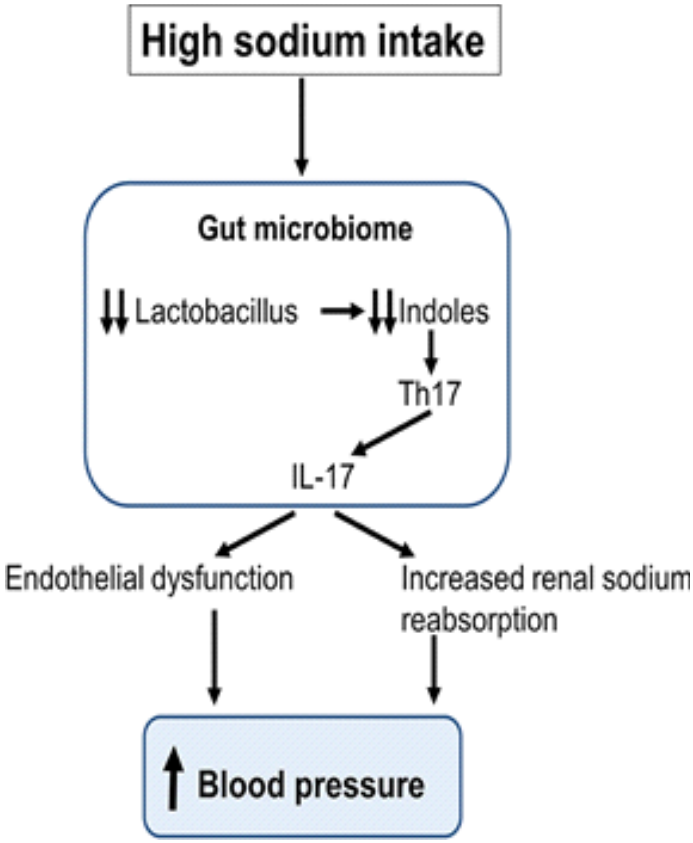
Source: Jeong HT, et al. High Blood Press. Cardiovasc. Prev. 2022; 29: 595-600; Nimmrich V, et al. Br. J. Pharmacol. 2013; 169: 1203-1210; Lovell MA, et al. Oxid. Med. Cell. Longev. 2015.;Wu CL, et al. Medicine. 2016: 95:32

NEW INSIGHTS ON THE ROLE OF SODIUM IN THE REGULATION OF BLOOD PRESSURE AND DEVELOPMENT OF HYPERTENSION

Intake of salt is a biological necessity, however excessive salt intake is associated with increase in the blood pressure by 4 to 10 mm Hg. It is estimated that hypertension will lead to 5 million deaths per year globally due to excessive salt intake.

A precise maintenance of sodium and fluid balance is an essential step in the regulation of blood pressure and alterations of this balance may lead to the development of hypertension.





Reducing salt intake lowers blood pressure, but processed foods contain "hidden" salt, which makes dietary control of salt difficult. In recent years, several new advances were made in our understanding of the interaction between sodium and blood pressure regulation.

The immune system plays a role, thereby supporting many previous studies indicating that the immune system is a crucial co-contributor to the maintenance of hypertension through pro-hypertensive effects in the kidney, vasculature, and brain.

Lastly, there is now evidence that sodium can affect the gut microbiome, and induce pro-inflammatory and immune responses, which might contribute to the development of salt-sensitive hypertension.

Current evidence supports a recommendation for moderate sodium intake in the general population (3–5 g/day). World Health Organization/United Nations has an objective of a 30% global reduction in sodium intake by 2025.

Source: Front. Cardiovasc. Med.Vol.6, Sept. 2019. S. Paolo; How Does Salt Intake Relate to Mortality? - Medscape – Sept.

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