Diabetes mellitus type 2 (DM2) results from the combination of insulin unresponsiveness in target tissues and the failure of pancreatic β cells to secrete enough insulin. It is a highly prevalent chronic disease that is aggravated with time, leading to major complications, such as cardiovascular disease and peripheral and ocular neuropathies.

Interestingly, therapies to improve glucose homeostasis in diabetic patients usually involve the use of glibenclamide, an oral hypoglycemic drug that blocks ATP-sensitive K+ channels (K<sub>ATP</sub>), forcing β cells to release more insulin to overcome peripheral insulin resistance. However, sulfonylureas are ineffective for long-term treatments and ultimately result in the administration of insulin to control glucose levels.

The mechanisms underlying β-cell failure to respond effectively with glibenclamide after long-term treatments still needs clarification. A recent study demonstrating that this drug activates TRPA1, a member of the Transient Receptor Potential (TRP) family of ion channels and a functional protein in insulin secreting cells, has highlighted a possible role for TRPA1 as a potential mediator of sulfonylurea-induced toxicity.

Some members from TRP family of ion channels have been related to the cationic non-selective currents in pancreatic β cells. TRPA1, a polymodal receptor that responds to noxius cold (< 17 °C), divalent cations (Ca<sup>2+</sup> and Zn<sup>2+</sup>), electrophilic compounds, and to polyunsaturated fatty acids, allows for Ca<sup>2+</sup> permeation into the cells where it is expressed. High expression of the TRPA1 channel has been shown in rat pancreatic islets and short-term treatments (≤ 1 h) with the agonists 4-hydroxy-2-nonenal (4-HNE), allylisothiocyanate (AITC) and 15-deoxy-Δ12,14-prostaglandin J<sub>2</sub>, result in a dose-dependent increase of cytosolic Ca<sup>2+</sup> with subsequent insulin release in RINm5F cells. Similar results have been reported for native β cells using the above mentioned agonists, as well as with H<sub>2</sub>O<sub>2</sub> and methylglyoxal (MG), suggesting that TRPA1 could be the link between inflammatory signals and oxidative metabolism and insulin secretion.

In a recent article published in the European Journal of Pharmacology, Babes and colleagues reported that glibenclamide acts as an agonist of the TRPA1 channel. The authors demonstrated that this sulfonylurea, but not tolbutamide, induces intracellular Ca<sup>2+</sup> transients in a dose-dependent fashion and increases cationic non-selective currents in HEK293 cells expressing human TRPA1 (hTRPA1). Moreover, these effects could be reversed by specific TRPA1 antagonists, and the authors also identified 3 critical cysteine residues at positions 621, 641, and 665 in the N-terminus for glibenclamide-mediated activation. Finally, they observed that glibenclamide increased intracellular Ca<sup>2+</sup> in a subpopulation of dorsal root ganglion (DRG) neurons (9% of the sample when applied at a concentration of 200 µM), although native channels from mice show a decreased affinity as compared with the heterologously expressed hTRPA1.

These results, as discussed in their paper, support a role for TRPA1 in some
of the glibenclamide-related side effects in diabetic patients, such as the development of abdominal pain and of a hyperactive bladder. In light of previous studies reporting TRPA1 expression in β cells, Babes and coworkers also suggested the potential participation of TRPA1 in the effects of glibenclamide as a secretagogue. This is not unlikely, since TRPA1 can promote insulin secretion in RINm5F cells when stimulated with the TRPA1 agonist AITC in the presence of the K\textsubscript{ATP} activator diazoxide, resulting in an increase of 35.5% compared with insulin secretion in the presence of diazoxide alone. However, the therapeutic impact of this phenomenon does not seem to be completely straightforward since it has been reported that treatment with glibenclamide can be rendered completely ineffective in patients carrying a mutation in the KCNJ11 (K\textsubscript{i6.2}) gene. This suggests that the possible “beneficial” activation of TRPA1 would not be able to overcome the glibenclamide resistance of K\textsubscript{ATP} channels to rescue a damaged glucose homeostasis. On the other hand, the results of Babes et al. shed light on the potential deleterious effects of long-term stimulation of TRPA1 channels by glibenclamide in patients with DM2.

Activation of TRPA1 by MG induces Ca\textsuperscript{2+} transients and augments non-selective cationic currents in hTRPA1-transfected HEK293 cells and mouse sensory neurons. In the same study, it was demonstrated that incubation with MG (10 mM for 20 min) reduces conductance velocity and amplitude of compound action potentials from wild-type but not from TRPA1\textsuperscript{−/−} mice, which could be relevant per se in the development of diabetic neuropathy. Beta-cell damage by glibenclamide is also a well-documented event that may sensitize or act synergistically to activate TRPA1. There are some arguments that glibenclamide may not be responsible for β-cell failure, since incubating INS-1 cells with various concentrations of glibenclamide during 24 h, in a glucotoxic environment, did not cause a significant increase in apoptosis. However, this observation contrasts with an overwhelming amount of evidence pointing to glibenclamide as a key player of β-cell exhaustion. More studies are needed to disregard possible differences between insulinomas and primary β cells, as well as differences among cell lines, but mainly to understand the complexity of the effectors at play in DM2.

In conclusion, the study of Babes and colleagues has identified glibenclamide as a novel activator of TRPA1, providing insights into some adverse effects observed in diabetic patients treated with this drug. This article supports the presence of another pathway responsible for the insulinotropic actions of glibenclamide, since both inhibition of K\textsubscript{ATP} channels and activation of TRPA1 could result in increased insulin secretion. Moreover, the results reported in this study could explain the initial exacerbation of hyperinsulinism in glibenclamide-treated DM2 patients, but also the progressive deterioration of β-cell function.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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