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Title: Idebenone and T2D: a new insulin-sensitizing drug for personalized therapy

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Insulin resistance is a characteristic feature of type 2 diabetes (T2D) that affects more than 30 million individuals in USA and more than 100 million worldwide. Insulin resistance occurs at several tissues, including skeletal muscle, liver, and adipocytes and plays a major role in the insurgence and in the pathogenesis of the diseases [1]. Indeed, the defect of insulin action in several tissues, including skeletal muscle and adipose tissue, is considered an early alteration in T2D, which is then followed by β-cell failure and hyperglycemia onset [1]. Several factors may alter insulin function [2], however, the final mechanism is not completely understood. To control glucose metabolism, insulin binds to insulin receptor (IR), a transmembrane protein which phosphorylates and recruits different substrate adaptors such as the cytoplasmic insulin receptor substrate (IRS) family of proteins. However, the IR also binds intracellularly to Src Homology 2 domain-containing transforming protein C1 (Shc) proteins, thus determining a decrease insulin sensitivity through a competition with IRS1 [2]. Of note, in diabetic patients, Shc expression levels are increased, and this increment is a consequence of several factors, including poor diet [3]. Therefore, from a therapeutic point of view, the identification of a molecule capable of favoring the binding of IR to

IRS1 may be an innovative option to increase the insulin sensitivity in T2D patients. In the current issue of *Pharmacological research*, Cortopassi et al, identified idebenone as a molecule able to facilitate the binding of IR to IRS1, thus sensitizing cell to insulin. Indeed, after the screening of several drugs, authors demonstrated in *vitro* and in *vivo* that idebenone, an analogue of coenzyme Q10 that is currently used to treat neurodegenerative diseases such as Alzheimer, is able to bind the Shc proteins (particularly the p52Shc), thus preventing Shc competition with IRS1 for IR. The insulin binding to IR determines the phosphorylation of tyrosine 960 within the IR juxtamembrane domain that is the site for which both p52Shc and IRS1 protein compete [4]. Idebenone administration, by blocking the negative effects of Shc on IR signaling, facilitate the physiological IR/IRS1 binding, thus resulting in a strong insulin response downstream, as showed by Cortopassi et al. Authors demonstrated, by co-immunoprecipitation, BLI for idebenone-Shc binding, Western Blots and in *vivo* analysis, that idebenone has positive cryoprotective effects mediated trough Shc protein inhibition. Importantly, authors observed that these positive effects are reached at a blood concentration of drug that is 50-fold lower than those that alter mitochondrial activity, since it is known that idebenone has a role in the mitochondrial electron transport chain and in the production of ATP. Interestingly, authors suggested that idebenone supplemental administration may be useful in T2D patients on metformin that are also treated with glucocorticoids for inflammation conditions (for diseases such as. arthritis, Crohn's disease, Lupus etc), in which the insurgence of insulin resistance is frequent. Defect of glucose up-take due to cellular insulin resistance is a crucial aspect of T2D and the facts that idebenone administration, by favoring the interaction between IRS1 and IR, will improve the cellular glucose control in these patients may have a significant impact on T2D outcome. Therefore, clinical trials looking at potential beneficial impact of idebenone treatment in T2D patients are required, as currently done to test the security and the efficacy of idebenone in patients affected by Multiple Sclerosis [5], and other diseases [6]. Downside effects of this clinical strategy for T2D patients must be carefully evaluated, since idebenone treatment may alter the activation of specific signaling pathways leading to long term side effects. Indeed, it is known that

Shc proteins are involved in the maintenance of the homeostasis of the heart [7] and have been indicated as one of the negative regulators of immunity inflammation and lymphocyte activation [8]. Of note, the role of immunity inflammation is becoming evident in T2D as well as in T1D [9, 10] and in other pathologies [11]. Moreover, it is important to test the best strategy to delivery of the drug since idebenone is characterized by poor water solubilization and lipophilicity, that may alter idebenone bioavailability in human. In conclusion, avoiding Shc competitive binding with IR through administration of idebenone may represent a novel therapeutic tool for insulin resistance and T2D.

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