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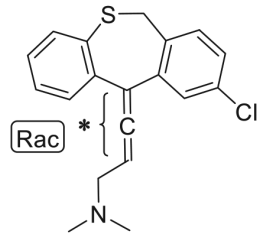
In This Issue of *Diabetes*

By Max Bingham, PhD

Chemical Scaffold Identified to Potentially Reverse β-Cell Dysfunction Due to Glucolipotoxicity in Diabetes

A phenotypic screen designed to identify low-molecular-weight compounds that protect β-cells from glucolipotoxicity (GLT) has identified a series of compounds that selectively block GLT-induced apoptosis. According to Vogel et al. (**p. 1032**), the mechanism of action involved likely centers on reducing calcium overload in islets that is induced by GLT, leading to enhanced β-cell survival. As a result, they suggest that such "calcium antagonists" may be the basis for a novel class of diabetes treatments and prevention drugs. The findings come from a phenotypic screening involving 312,000 compounds and various steps that included the elimination of candidates that were toxic or general apoptosis inhibitors and further narrowing to select candidates that had antiapoptotic effects in islets. The final step tested whether compounds could prevent GLT-induced reduction of glucose-stimulated insulin secretion in rodent and human islets. According to the authors, they identified one particular hit (see right) called "compound A." Further medicinal chemistry efforts separated out two enantiomers, which they further optimized to improve the viability and function of both rat and human islets under GLT conditions. Moving to mechanisms, the authors found that the compounds decreased GLT-induced cytosolic calcium influx in islets and that all of the further findings pointed toward this being the central mechanism of action. Commenting further, author Alina Berdichevsky told *Diabetes*: "The idea of calcium channel blockers conferring β-cell apoptosis protection is not novel. There is a growing number of literature reports indicating that certain calcium channel blockers improve β-cell function in patients with type 2 diabetes, i.e., when used for other indications, such as hypertension. Our study shows that at least in our model system, calcium overload is the central mechanism underlying the detrimental nutrient overstimulation of islet cells. It is tempting to speculate that calcium antagonists with properties that allow prevention of excessive calcium influx without blocking glucose-stimulated insulin secretion under normal conditions could be the elusive therapy improving β-cell health in type 2 diabetes."



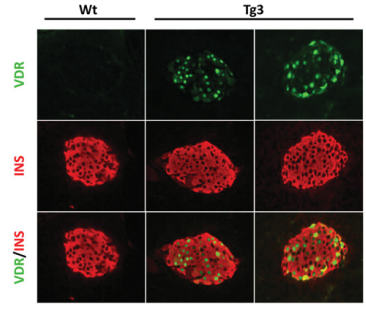
Compound A (racemic)

Structure of screening hit compound A. *Rac, chiral center of the racemic allene compound.

Vogel et al. A phenotypic screen identifies calcium overload as a key mechanism of β-cell glucolipotoxicity. Diabetes 2020;69:1032–1041

Vitamin D Receptor in Islets Downregulated During Diabetes Development

The expression of vitamin D receptor is downregulated in β-cells during the development of both type 1 and type 2 diabetes, according to Morró et al. (**p. 927**). Conversely, overexpression of the receptor somewhat protects against diabetes development, at least in mice. The results might help explain the mixed results that show vitamin D supplementation may or may not be beneficial in terms of glucose metabolism in diabetes. The conclusions come from an investigation into the role of the vitamin D receptor and potential mechanisms in terms of the development of diabetes. The authors found that gene expression for the receptor was reduced in islets from various mouse models of diabetes development. In parallel, they also reveal a trend in the same direction in human islets from healthy individuals and patients with type 2 diabetes. They also found that islets from transgenic mice overexpressing the receptor had higher levels of mRNA for the receptor than wild-type controls. Other features indicated the mice had normal glucose tolerance and insulin responses compared with controls and on a cellular level apparently similar levels of β-cells and islet numbers. However, when challenged with streptozotocin to induce diabetes, 100% of the wild-type mice transitioned to diabetes, while only 60% of the transgenic mice developed diabetes with a less severe form of hyperglycemia. Commenting further, author Alba Casellas told us: "This work reveals a role for vitamin D receptor in β-cell physiology and in protection from diabetes. The key question now is to understand how vitamin D receptor expression is controlled and, more specifically, what the mechanisms are underlying its decrease during diabetes, in particular in humans. This knowledge should help us to improve strategies for the treatment of diabetes based on vitamin D supplementation. Future studies should also address the potential causative role of β-cell vitamin D receptor downregulation in diabetes."



Detection of vitamin D receptor (green) specifically in insulin (red) positive β-cells of wild-type (Wt) and transgenic (Tg3) mice with receptor overexpression.

Morró et al. Vitamin D receptor overexpression in β-cells ameliorates diabetes in mice. Diabetes 2020;69:927–939

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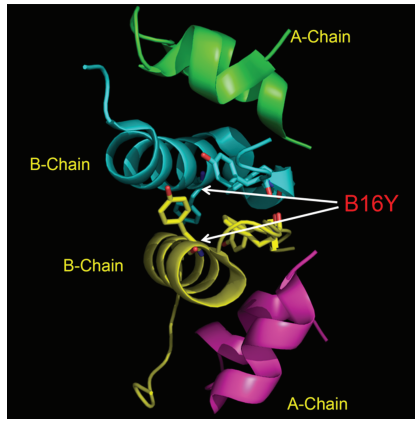
Proinsulin Interactions Explored as a Potential Drug Target for Diabetes

The proinsulin-proinsulin contact surface may be a potential drug target to prevent and delay the development of mutant *INS* gene–induced diabetes of youth, or MIDY, according to Sun et al. (**p. 954**). Currently, the underlying mechanisms of MIDY are thought to involve abnormal conformations of proinsulin and their interactions within the endoplasmic reticulum, which result in decreased β-cell mass. However, the actual molecular interactions are unknown, according to the authors. The findings come from experiments with various (pro)insulin mutants and an investigation into their effects on various cell types after cell transfection, metabolic labeling, immunoprecipitation, and various other assays. Based on their analyses, the authors suggest that misfolded versions of proinsulin, such as those that cause MIDY, can combine with wild-type proinsulin and together they effectively get stuck in the endoplasmic reticulum, halting the formation of insulin. Specifically, they found that a tyrosine residue at position 16 of the B-chain of proinsulin conferred a "dominant-negative" behavior of a MIDY proinsulin termed C(A7)Y. By replacing this tyrosine with alanine or aspartic acid, they found the changes resulted in a decrease of abnormal interactions between the different proinsulin types. This resulted in wild-type proinsulin export being rescued, reduced endoplasmic reticulum stress, and increased insulin production in β-cells and human islets. Commenting further, author Peter Arvan told *Diabetes*: "Here we limited toxic proinsulin interactions by mutagenesis, but our goal is to achieve a similar outcome with proinsulin dimerization surface protectors to rescue forward transport of proinsulin, with reduced endoplasmic reticulum stress and enhanced insulin production." Author Ming Liu added: "In addition to proinsulin, many secretory proteins dimerize in the endoplasmic reticulum. It would be interesting to explore whether heterodimerization of wild-type and disease-causing mutant proteins in the endoplasmic reticulum is an underlying molecular mechanism of other congenital dominant diseases caused by mutant secretory proteins."



Insulin dimer with tyrosine residue at position 16 of the B-chain (B16Y) highlighted near the center of the homodimerization surface.

Sun et al. Role of proinsulin self-association in mutant *INS* gene–induced diabetes of youth. Diabetes 2020;69:954–964

Risk Factors Identified for Neuropathy Complications in Type 1 Diabetes

Higher long-term cumulative glycemic exposure, as measured by HbA_{1c}, is the strongest independent risk factor for diabetic peripheral neuropathy (DPN) in type 1 diabetes, according to Braffett et al. (**p. 1000**). Raised HbA_{1c} is also the strongest modifiable risk factor for cardiovascular autonomic neuropathy (CAN), according to the authors, although they also identify many other factors that might be involved in neuropathy outcomes in type 1 diabetes. The findings come from further analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The authors looked at multiple risk factors and phenotypic characteristics associated with the different neuropathies, taking in data from a mean follow-up of 23 years. Over the duration of the study, 33% of DCCT/EDIC participants developed DPN and 44% developed CAN. In addition to higher HbA_{1c} as a key risk factor for DPN, the authors also found associations with older age, longer duration of disease, greater height, kidney disease, higher pulse rate, and β-blocker use. In terms of CAN, older age and higher HbA_{1c} were the most significant risk factors, followed by kidney disease and longer duration of disease. Other factors associated with CAN included higher pulse rate, higher systolic blood pressure, β-blocker use, and cigarette smoking. Commenting further, authors Barbara H. Braffett and Rodica Pop-Busui told us: "Standardized assessments of risk factors and neuropathy outcomes over more than 20 years of follow-up in the DCCT/EDIC study provide a unique opportunity to assess risk factors for advanced neuropathy complications in type 1 diabetes and further complement our findings for cardiovascular, renal, and eye outcomes. While for many years decreasing HbA_{1c} has been considered the focus for reducing the risk of complications in type 1 diabetes, these comprehensive analyses have identified additional risk factors, some modifiable, which help us in understanding different patient phenotypes for neuropathy. Aggressive glycemic management coupled with aggressive management of other nonglycemic risk factors are recommended to reduce the burden of neuropathy in individuals with type 1 diabetes."

Braffett et al. Risk factors for diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. Diabetes 2020;69:1000–1010

https://doi.org/10.2337/db20-ti05