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DIABETES

Getting personal with type 2 diabetes mellitus—from genetics to targeted therapy

Research published in *Science Translational Medicine* has demonstrated that defective insulin secretion in patients with type 2 diabetes mellitus (T2DM) who carry a genetic risk variant in the gene that codes for the α_{2A}-adrenergic receptor (α_{2A}AR; encoded by *ADRA2A*) can be successfully treated with an α_{2A}AR antagonist. These findings suggest that the reality of developing personalized therapies on the basis of an individual's genetic makeup is closer than ever before.

In 2010, a research team from Lund University, Sweden, led by investigator Anders Rosengren, made a pioneering discovery that linked the genetic variant rs553668 in the *ADRA2A* gene to a specific disease mechanism for T2DM: they showed that the presence of rs553668 was associated with overexpression of α_{2A}AR and suppression of insulin secretion. Blocking α_{2A}AR with yohimbine resulted in improved insulin secretion in pancreatic islet cells from organ donors who carried the risk variant.

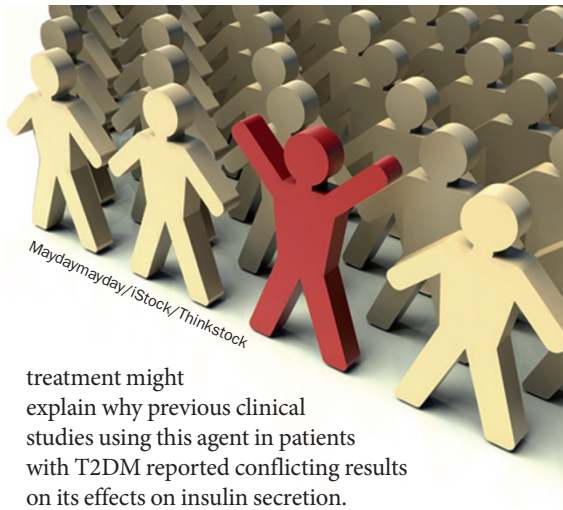
In the new study, the researchers have extended their findings by treating patients with T2DM who harbour the rs553668 variant with yohimbine. In total, 50 patients with T2DM were enrolled in the study, including 21 who did not carry the risk allele, 21 patients who were heterozygous for the allele and seven patients who were homozygous for the allele. One patient did not continue participation after the initial screening visit and two patients were excluded from the study after experiencing adverse reactions following yohimbine treatment.

A dose-escalation study design was implemented—each patient received 0 mg (placebo), 10 mg or 20 mg of yohimbine orally in a randomized double-blind fashion over three visits spaced 2 weeks apart. Every patient received all doses of the drug, and the protocol was designed so that no patient received the 20 mg dose before the 10 mg dose. An oral glucose tolerance test was performed 1 h after each treatment. As the rs553668 risk allele had been previously associated with impaired insulin secretion 30 min after glucose intake during an oral glucose tolerance test (Ins30), the effects of 20 mg of yohimbine on Ins30 were used as the primary variable assessed in the study.

Considered together, patients who were either heterozygous or homozygous for the risk allele had a 25% reduction in baseline Ins30 compared with patients who did not have the risk allele. All patients carrying the rs553668 risk variant showed marked improvements in Ins30 following treatment with yohimbine when compared with placebo intake. Moreover, the treatment effects were dose-dependent, with improvements in plasma levels of insulin of 20% and 29% following treatment with 10 mg and 20 mg of yohimbine, respectively. By comparison, yohimbine treatment in the group of patients who did not have the risk allele was ineffective, as no significant differences in Ins30 were observed in these patients when the 20 mg dose was compared with placebo intake.

The contribution of allelic dosage to the stimulatory treatment effects was also substantial, as revealed by the comparison of responses to treatment in individuals who were either heterozygous or homozygous for the risk allele. A 14% increase in Ins30 stimulation per risk allele was reported following administration of 10 mg of yohimbine ($P = 0.04$ using linear regression with correction for age, sex and BMI); treatment with 20 mg of yohimbine resulted in an increase in Ins30 stimulation of 16% per risk allele ($P = 0.04$). Analysis using a linear interaction model further confirmed that the observed effects on Ins30 stimulation were dependent on both the dose of yohimbine and the number of risk alleles carried by an individual.

The finding that only those patients with the risk allele were responsive to yohimbine treatment might explain why previous clinical studies using this agent in patients with T2DM reported conflicting results on its effects on insulin secretion.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Fasting glucose levels at baseline and glucose levels 30 min following treatment with 20 mg yohimbine were improved in all study participants, possibly as a result of the treatment having pleotropic effects. However, at 120 min no effects were observed on either insulin or glucose levels, which is likely to be attributable to the short half-life of the drug.

Rosengren has high hopes for the development of personalized therapies: "Future T2DM treatment will have lifestyle changes as a cornerstone, supported by combinations of drugs that will specifically interfere with the pathophysiology of the disease based on genetic risk variants or other biomarkers."

The research group plans to continue their investigations by testing this treatment approach in cohorts with increased numbers of participants. Additionally, they are looking to develop partners to modify yohimbine with the aim of ameliorating adverse effects associated with this therapy, such as anxiety and elevated blood pressure.

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Original article Tang, Y. *et al.* Genotype-based treatment of type 2 diabetes with an α_{2A}-adrenergic receptor antagonist. *Sci. Transl. Med.* doi:10.1126/scitranslmed.3009934