DIABETES

Dextromethorphan stimulates insulin secretion from pancreatic β cells—a new role for an old drug?

New research published in *Nature Medicine* reveals that dextromethorphan, which is an active ingredient in many over-the-counter cough suppressant medicines, can improve survival of pancreatic islet cells and increase glucose-stimulated insulin secretion (GSIS). These effects occurred via antagonism of N-methyl-D-aspartate (NMDA) receptors, which suggests that these receptors could be targeted during drug development for type 2 diabetes mellitus (T2DM).

The team of researchers from Düsseldorf, Germany, led by Eckhard Lammert (Heinrich Heine University), initially proposed that dextromethorphan might be a useful treatment for paediatric patients with hyperinsulinaemia. In collaboration with Thomas Meissner (University Children's Hospital Düsseldorf), the researchers formulated this original hypothesis on the basis of findings published in 2000 that reported the cases of two children with severe bacterial meningitis who developed insulin-dependent diabetes mellitus after treatment with a high dose of dextromethorphan.

The functions of NMDA receptors in the nervous system are well characterized; however, their role in islet cells remains

controversial. Thus, in order to closely examine the relationship between dextromethorphan, NMDA receptors and GSIS in islet cells, Lammert and his team conducted a careful analysis using genetically altered mice, pharmacological agonists and antagonists of NMDA receptors and a small proof-of-concept study in patients with T2DM.

Islet cells from mice carrying a pancreatic-epithelium-specific deletion of *Grin1*, which encodes the glutamate receptor, ionotropic, NMDA 1 subunit, had a 60–80% reduction in *Grin1* expression compared with islets from control heterozygous littermates. Surprisingly, rather than the expected decrease, *Grin1*-deficient islets showed increased GSIS in an *in vitro* assay. This finding was supported by observations that *Grin1*-deficient mice had similar basal blood glucose concentrations, but improved glucose tolerance compared with control animals.

Incubation of wild-type mouse islet cells with NMDA receptor antagonist MK-801 increased GSIS, but did not have an effect on total insulin content of the islets. Conversely, treatment of mouse islets with NMDA, which is an agonist of these receptors, showed no effect on insulin release. Together, these findings demonstrate that NMDA receptors limit GSIS, but not basal levels of insulin secretion, and have no effect on insulin production in islet cells. Furthermore, MK-801 elongates membrane potentials in β cells and the effects of MK-801 on insulin release were dependent on expression of KATP channels.

Treatment of mouse and human islets with the clinically relevant compound dextromethorphan, and its primary metabolite, dextrorphan, produced results similar to those of studies with the pharmacological inhibitor. Furthermore, overnight supplementation of drinking water with dextromethorphan resulted

in no changes to basal plasma levels of insulin or fasting glucose levels of mice, but did cause increased glucose tolerance and glucose-induced plasma insulin concentrations in treated animals compared with non-treated mice.

In mice deficient for the leptin receptor, which develop T2DM by the age of 1–2 months, treatment with a high dose of dextromethorphan (3 mg/ml) led to lower fasting blood glucose levels, slower progression to hyperglycaemia and improved glucose tolerance compared with treatment with a low dose (1 mg/ml). Islets from animals treated with the high dose had higher insulin content and lower numbers of apoptotic cells than low-dose treated mice.

The investigators conducted a phase IIa, double-blinded, placebo-controlled, randomized, fourfold crossover single-dose proof-of-concept study that included 20 men with T2DM who were receiving metformin monotherapy. A well-tolerated dose of dextromethorphan (60 mg) was sufficient to considerably increase serum concentrations of insulin and even a dose of 270 mg reduced glycaemic excursions in an oral glucose tolerance test compared with placebo in the same individuals.

The findings reported in this study are promising. Although Lammert admits that it will take time to develop dextromethorphan into an official anti-diabetic drug, he remains optimistic. “Things might go faster, as this drug has been in use in the USA as an over-the-counter medication for more than five decades, is now in use for long-term treatment of other diseases and is still considered to be quite safe,” he explains.

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