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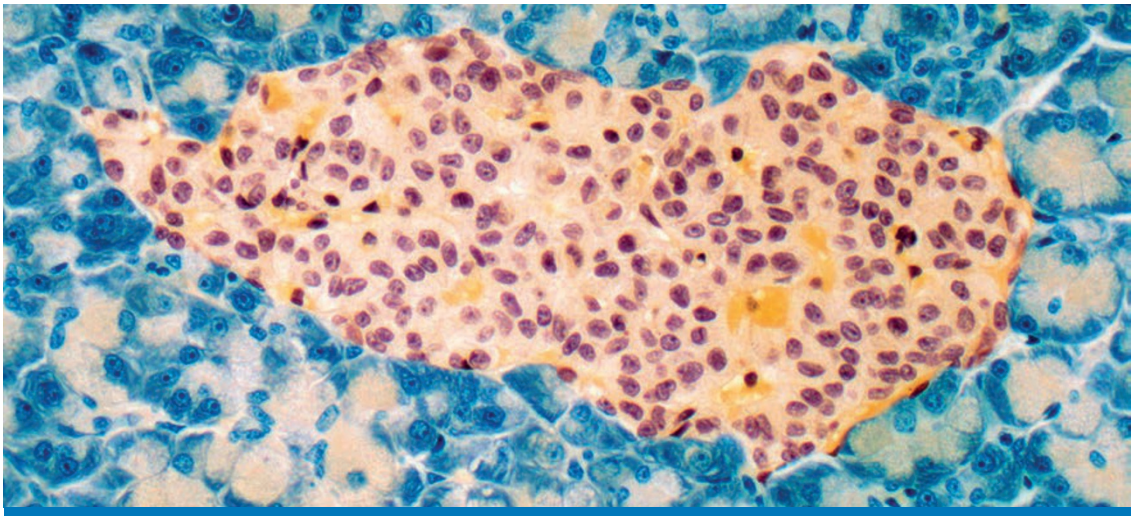

STEVE GSCHMEISSNER

RISK FACTORS

Melatonin signalling implicated in the risk of T2DM

A common variant of the gene that encodes the melatonin receptor 1B (*MTNR1B*) is known to be associated with an increased risk of developing type 2 diabetes mellitus (T2DM). Now, the mechanisms underlying this association have been revealed in a new study published in *Cell Metabolism*.

"Importantly, while more than a hundred gene loci have been reported to be associated with T2DM, in very few instances has a molecular mechanism been elucidated and proven to be accountable for genetic association with the disease," explains corresponding author Hindrik Mulder. "It is essential to understand why a genetic variant is linked to a disease, especially if you want to develop new drugs that help patients." To elucidate the link between the rs10830963 variant of *MTNR1B* and T2DM, Mulder and colleagues conducted a series of experiments in isolated human islets, cell lines, mice and humans.

The researchers used RNA sequencing to demonstrate that human carriers of the risk allele had increased expression of *MTNR1B* mRNA in their pancreatic islets, which establishes the locus as an expression quantitative trait locus. Next, the team used an adenovirus to drive overexpression of *MTNR1B* in insulin-secreting INS-1 832/13 cells. Insulin release was normal in these cells. However, the addition of melatonin reduced insulin secretion more extensively from cells overexpressing *MTNR1B*. Furthermore, the team demonstrated that the addition of melatonin led to reduced formation of cAMP in the cells overexpressing *MTNR1B*, which they identify as the mechanism underlying the reduction in insulin release.

Interestingly, experiments in mice showed that knockout of *Mt2* (the mouse equivalent of *MTNR1B*) led to increased insulin secretion and greater β-cell mass compared with wild-type littermates. Levels of cAMP were increased in $Mt2^{-/-}$ mice, which the authors suggest is the result of the lack of the inhibitory effect of melatonin.

The investigators then recruited 45 nondiabetic individuals — 23 with two copies of the risk allele (GG) and 22 with two copies of the nonrisk allele (CC). All participants were given 4 mg of melatonin at bedtime for 3 months, and then underwent an oral glucose tolerance test. Insulin release and glucose concentrations were decreased in all participants, but the effect was more marked in the GG carriers than in the CC carriers. In addition, GG carriers had reduced insulin secretion after the melatonin treatment, compared with baseline.

Mulder and co-workers suggest that these findings indicate that increased melatonin signalling in islet cells reduces insulin secretion, which leads to hyperglycaemia and an increased risk of developing T2DM. The team are continuing to explore the mechanisms underlying the effects of melatonin in islet cells. "Future studies of risk variant carriers and their susceptibility to the metabolic risks of shift work and jet lag are warranted," concludes Mulder.

Claire Greenhill

> "…increased melatonin signalling in islet cells reduces insulin secretion…"

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