Melatonin signaling is a risk factor for type 2 diabetes

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A sleeping pancreas releases less insulin, but how much insulin drops each night may differ from person to person, suggests a study published May 12, 2016 in *Cell Metabolism*. Up to 30 percent of the population may be predisposed to have a pancreas that's more sensitive to the insulin-inhibiting effects of melatonin, a circadian rhythm hormone. People with this increased sensitivity carry a slightly altered melatonin receptor gene that is a known risk factor for type 2 diabetes.

Large-scale studies have identified over 100 genes related to an increased risk of developing type 2 diabetes—a disorder in which someone has abnormally high blood sugar levels due to a lack of insulin. On the list of risk factors is a single change to the melatonin receptor gene *MTNR1B*, found in 30 percent of the population. It's known that the *MTNRIB* receptor makes cells sensitive to melatonin, but Hindrik Mulder of Lund University in Sweden and Leif Groop, of Lund University and the University of Helsinki in Finland wanted to understand what this gene variant could be doing in the pancreas.

"Type 2 diabetes is a polygenetic disease, so it's not one gene that causes the disease: there are probably hundreds of genes that jointly predispose individuals, from which you can infer that the contribution of each individual gene will be quite small," says Mulder, co-senior author on the study, whose lab studies the pancreas.

The researchers present data from pancreatic islets derived from humans who have one or two copies of the risk variant of the *MTNR1B* gene. Those who have two copies have higher levels of the melatonin receptor than those with one or no copies. This increase in melatonin receptors makes a person's pancreas more sensitive to melatonin.

In follow-up experiments, the researchers used insulin-secreting cells and mouse islets to increase or decrease the number of melatonin receptors on insulin-producing beta cells. As expected, mice and islets with very few melatonin receptors secreted more insulin in the presence of high levels of melatonin compared to those with many melatonin receptors, from which less insulin was secreted.

Mulder and Groop then tested their hypothesis on 23 non-diabetic people with the *MTNR1B* risk gene variant and 22 people without. They asked each person to take 4 milligrams of melatonin (about the amount found in commercial pills) at bedtime for three months. By the end of the study, individuals without the risk gene variant had three times the level of insulin secretion than those with the gene variant.

The researchers say that this doesn't mean that the occasional melatonin pill is necessarily dangerous for the one in three people with the *MTNR1B* risk gene variant or that anyone should rush out and get a genetic test to see if they are carriers. "This is just a hypothesis, but I think it raises questions that maybe prolonged use of melatonin is not so harmless," Mulder says.

The results make sense, he adds, since melatonin is a known hormone that helps the body keep time. "We don't typically eat or are physically active at night, so our energy demands drop and we don't need maximum insulin secretion," Mulder says. "A likely explanation is that, as melatonin levels rise, they tell our beta cells not to release as much insulin." Another hormone, glucagon, is also known to ensure that glucose levels in the blood are sufficient when we do not eat, for instances during the night.

The researchers will continue to explore the relationship between type 2 diabetes risk genes and the pancreas. They hope their studies will help inform future approaches to personalized medicine.

More information: *Cell Metabolism*, Tuomi, Nagorny, Singh et al.: "Increased melatonin signaling is a risk factor for Type 2 Diabetes" www.cell.com/cell-metabolism/f … 1550-4131(16)30160-7 , DOI: 10.1016/j.cmet.2016.04.009