

A diabetes drug, sitagliptin, also has a potential to prevent diabetes

Diabetes type 2 is caused by insufficient levels of insulin to keep blood glucose under control. Excessive levels of another hormone, glucagon, can also contribute to diabetes type 2 by causing the liver to flood the body with stored glucose. Diabetes type 2 does not arise overnight, but slowly progresses for many years as a condition known as prediabetes. In prediabetes, blood sugar rises to excessive levels after a meal, but is normal or nearly normal after an overnight fast. Researchers are seeking ways to prevent prediabetes from progressing to diabetes. Besides diet and exercise, the diabetic drug metformin can slow the onset of diabetes.

On page 309 of this issue of *Experimental Biology and Medicine*, researchers in the Department of Nutrition at Case Western Reserve University determined whether a newer diabetes drug, sitagliptin, might be effective in prediabetes. Sitagliptin works by boosting the levels of an intestinal factor known as GLP-1. This factor increases insulin output while also decreasing glucagon output. They used an animal model with prediabetes, the SHROB rat, which was developed at Case Western Reserve University beginning in the 1970s. These rats are extremely obese and have normal glucose after fasting but high glucose after a meal, like prediabetic humans. Also like prediabetic humans, they have excessive levels of glucagon.

The prediabetic rats were divided into three groups and treated with either a placebo, sitagliptin, or another older diabetes medication, glyburide, which acts by boosting the production of insulin by the pancreas. Sitagliptin and glyburide were equally effective in lowering glucose levels after a meal. Surprisingly, only sitagliptin raised the total

output of insulin by the pancreas and only sitagliptin lowered glucagon to normal levels.

Neither of the diabetes medications had any effect on body weight, total body fat or food intake. This matches studies in humans, which show no loss or gain of weight from these drugs. But differences appeared when the distribution of body fat was examined. Compared with the older drug glyburide, sitagliptin caused a redistribution of body fat from the abdominal fat deposits to deposits under the skin. Lowering the proportion of fat stored within the abdomen has a number of favorable effects in diabetes and for cardiovascular risk factors. This is the first time that sitagliptin has been found to affect fat distribution, and the cellular basis for this change is an open question.

Group leader Paul Ernsberger, PhD, says, 'These animal studies suggest that sitagliptin should be tested in the clinic as a possible diabetes-preventing medication. It may act to shore up the function of the pancreas, which deteriorates during the onset of diabetes.' Co-investigator Richard J Koletsky, MD, says, 'Sitagliptin's effects on enhancing post prandial insulin secretion and decreasing glucagon secretion offer new pharmacologic interventions to combat diabetes and potentially delay and even prevent its onset.'

Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said, 'This animal model study by Ernsberger and colleagues suggests that sitagliptin can slow the onset of diabetes. Of great interest is the finding that this drug can redistribute body fat from the abdomen to deposits under the skin.'

DOI: 10.1258/ebm.2011.011f03