New insights into insulin resistance could lead to better drugs for diabetics

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Research published in the October *Molecular and Cellular Biology* moves us closer to developing drugs that could mitigate diabetes.

Diabetes afflicts an estimated 26 million Americans, while 79 million have prediabetes. In other words, one in three Americans confronts this disease. Diabetes raises the risk of heart disease and stroke by as much as fourfold, and it is the leading cause of blindness among adults 20-74. It is also the leading cause of kidney failure.

In earlier research, four years ago another team of researchers showed that they could boost insulin sensitivity in experimental rodents by giving the animals a drug called myriocin. People with diabetes have a condition called insulin resistance, which renders them poorly able to process sugar. That results in high blood sugar, which damages the blood vessels, leading to many of diabetes' ills. In their study, that team, led by Johannes M. Aerts of the University of Amsterdam, observed a decrease in a compound called ceramide, which sits on cell membranes in the circulatory system, which they postulated was responsible for the rise in insulin sensitivity.

In the new study, Xian-Cheng Jiang of Downstate Medical Center, Brooklyn, NY, and his collaborators set out to confirm this earlier work, using a genetic approach.
The new research provides strong evidence that ceramide was not causing insulin sensitivity, but that another membrane-bound compound, sphingomyelin, might be doing so.

Ceramide is the substrate for the last step in a five step cascade that produces sphingomyelin. In that step an enzyme called sphingomyline synthase 2 (SMS2) cleaves ceramide to produce sphingomyelin. The first enzyme in this pathway is called serine palmitoyltransferase (SPT).

To test the hypothesis that ceramide is involved in modulating insulin resistance the researchers used knockout mice for each of these enzymes. They postulated that (partially) knocking out the first enzyme in the cascade would decrease ceramide levels while knocking out the last enzyme in the sphingomyelin pathway would boost ceramide levels, since that enzyme uses ceramide to produce sphingomyelin. Thus, SPT knockout mice would have greater insulin sensitivity, while SMS knockout mice would have reduced insulin sensitivity.

Surprisingly, while ceramide levels changed as predicted, that change did not influence insulin sensitivity, which was higher in both groups.

The research has important implications for drug development for mitigating diabetes. Myriocin proved highly toxic and major efforts to modify the drug to reduce that toxicity have been fruitless. Myriocin's toxicity probably stems from the fact that it inhibits the first step of the sphingomyelin biosynthetic pathway, affecting all the downstream biology, says Jiang. The discovery that knocking out the last step in the biosynthetic pathway improves insulin sensitivity means that drug treatments could target that last enzyme, SMS, leaving the rest of that biosynthetic pathway to function normally.

More information: Z. Li, et al., 2011. Reducing plasma membrane sphingomyelin increases insulin sensitivity. *Mol. Cell. Biol.* 31:4205-4218.