SEPTEMBER 2016

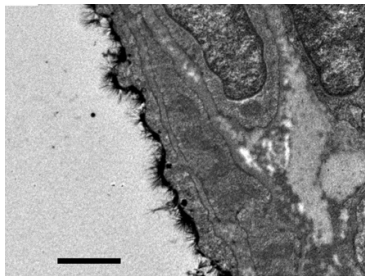
diabetes®

In This Issue of *Diabetes*

By Max Bingham, PhD

Hyaluronidase Linked to Endothelial Dysfunction in Diabetes

An enzyme that normally breaks down the major extracellular matrix component hyaluronan may be the key to explaining various vascular complications in diabetes. In particular, it seems likely that hyaluronidase activity exacerbates endothelial dysfunction in diabetes. The study by Dogné et al. (**p. 2742**) focuses on HYAL1 knockout mice and control wild-type mice and examines the effect of HYAL1 on endothelial (dys) function markers in the presence or absence of streptozotocin-induced diabetes. Specifically they examined the effects of the deletion on endothelial markers, endothelial-dependent vasodilation, arteriolar glycocalyx size, and glomerular barrier function. According to the authors, the lack of HYAL1 conferred a number of beneficial effects in the mice when diabetes was also present. In terms of endothelial dysfunction, the lack of HYAL1 prevented increases in P-selectin (a cell adhesion molecule) while a measure of vasodilation suggested better protection in the knockout mice. Glycocalyx thickness and structure (as well as hyaluronan content) were also better preserved in the presence of diabetes in the knockout mice as compared to the wild-type mice. The lack of HYAL1 also completely prevented diabetes-induced glomerular barrier dysfunction (where the kidney's ability to filter blood becomes impaired), further suggesting beneficial effects toward glycocalyx preservation. As for mechanisms, the authors suggest the absence of the HYAL1 enzyme prevents glycocalyx from shedding hyaluronan during diabetes and this in turn prevents a whole series of events leading ultimately to vascular damage and attendant (clinical) complications. Commenting more widely on the study, author Sophie Dogné said: "The expression of the hyaluronidase enzyme, HYAL1, is increased in all forms of diabetes, whether experimental or human diabetes. Our study suggests this increase is linked to early endothelium and glycocalyx damage. We intend to test HYAL1 inhibition as a means to prevent endothelial damage in diabetes. This is a new therapeutic approach that has not been envisaged, or even tested, so far."

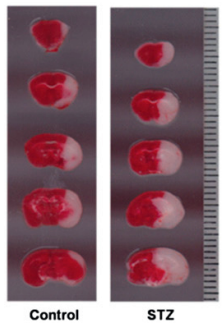


TEM image of glycocalyx in myocardial arterioles of HYAL1 knockout mice.

Dogné et al. Hyaluronidase 1 deficiency preserves endothelial function and glycocalyx integrity in early streptozotocin-induced diabetes. Diabetes 2016;65:2742–2753

Safety of Sulfonylureas in Type 2 Diabetes: Risk of Stroke and the KATP Channel

Sulfonylureas used as antidiabetes treatments may carry an increased risk of stroke in patients with type 2 diabetes, according to a meta-analysis by Liu et al. (**p. 2795**). On top of this, additional studies by the authors suggest that the drug may inhibit the ATP-sensitive potassium (K_{ATP}) channel, which is a key pathway involved in neuroprotection. The experiments focused on mice with induced diabetes or controls that were subjected to a middle cerebral artery occlusion (a mouse model for a stroke). The diabetic mice had far greater levels of brain damage and neurological deficits following the induced stroke. Consistently, various proteins involved in a stroke were also up- or downregulated. Additional experiments in mice (but this time on nondiabetic mice, due to the extra severity of the procedure imposed) showed that prior administration of the sulfonylurea K_{ATP} channel blocker resulted in substantially more damage following an administered stroke. Conversely, less damage occurred when a K_{ATP} channel opener was administered prior to a stroke. Neurological deficits in the mice where either higher or lower depending on whether a channel blocker or opener was given. The researchers report that taken together their experimental data and meta-analysis suggest the K_{ATP} channel might be a target for neuroprotection in a stroke and that sulfonylurea use in type 2 diabetes "should be considered carefully or even avoided." Authors Zhong-Ping Feng and Hong-Shuo Sun told *Diabetes Care*: "Stroke and diabetes are leading causes of mortality and disability in chronic diseases globally. Considering people with diabetes have a higher risk of stroke, it is critical to understand the reasons for higher stroke risk in diabetes. Importantly, this may include the treatments that diabetic patients receive. Further studies are needed not only to identify the causal relationship between antidiabetes drugs and stroke risk, but also to develop new strategies in diabetic therapy."



Effects of STZ-induced diabetes in the tMCAO mouse model: normal brain tissue is red and infarcted brain tissue is white.

Liu et al. Cerebrovascular safety of sulfonylureas: the role of K_{ATP} channels in neuroprotection and the risk of stroke in patients with type 2 diabetes. Diabetes 2016;65:2795–2809

SEPTEMBER 2016

diabetes®

Adipocytokine NOV/CCN3: A New Target for Obesity-Related Insulin Resistance?

Martinerie et al. (**p. 2502**) report this month on NOV/CCN3, which they say is a new adipocytokine that is likely involved in obesity-associated insulin resistance. According to the authors, the NOV/CCN3 gene (nephroblastoma overexpressed gene) and resulting NOV/CCN3 protein plasma levels are reportedly highly correlated with BMI. However, little is known about the role of NOV/CCN3 in energy homeostasis. On that basis they report a series of experiments in mice designed to uncover the role of NOV/CCN3 in adipose tissue and whole-body metabolism. To do this, the authors investigated the effect of targeted deletion of *nov* genes and the subsequent effects in mice fed a normal or obesogenic diet. Reportedly, when fed a high-fat diet, the knockout $NOV^{-/-}$ mice put on less weight than the control wild-type mice. However, this did not happen when fed a standard diet (there was no difference in weight gain between the groups). The lower weight gain on the high-fat diet in the knockout $NOV^{-/-}$ mice appeared to be related to a significant reduction in fat mass (despite the high-fat diet) that was associated with an increased proportion of smaller adipocytes and significantly higher expression of genes involved in energy expenditure. Reportedly, the knockout mice were also more active during daylight hours. At the same time, the knockout mice had improved glucose tolerance and insulin sensitivity and an immunological profile that suggested reduced inflammation. A significant proportion of the effects of obesity are thought to involve proinflammatory processes. Commenting more widely on the study, author Bruno Fève stated: "In the near future, the main challenges will be to establish NOV involvement in the pathogenesis of insulin resistance in obese or type 2 diabetic individuals and to understand the mechanisms by which this new adipokine signals in adipose tissue and induces a browning of white adipose tissue. Much work is needed before considering the potential therapeutic interest of this protein."

Martinerie et al. NOV/CCN3: a new adipocytokine involved in obesity-associated insulin resistance. Diabetes 2016;65:2502–2515

Metabolic Signature to Predict Transition of Gestational Diabetes Mellitus to Type 2 Diabetes

A new signature composed of a variety of metabolites in plasma might predict the progression of gestational diabetes mellitus (GDM) to type 2 diabetes according to a study by Allalou et al. (**p. 2529**). Assuming the predictive ability can be improved from an already high 77–83% and the approach is developed further, the authors suggest this might spell the end to complicated and often inaccurate methods currently used to monitor GDM/type 2 diabetes transition. They even suggest the approach might replace current tests with a much faster version based on one blood sample. The study deployed metabolomics, a technique that attempts to identify predictive signatures of disease based on large data sets relating to metabolites in biological samples. Focusing on a prospective cohort of 1,035 women with GDM (the Study of Women, Infant Feeding, and Type 2 Diabetes Mellitus After GDM Pregnancy [SWIFT]), they identified 130 patients that progressed to type 2 diabetes within four years. The authors used a case-control approach to report the screening of baseline blood samples for 182 metabolites using a variety of techniques. Subsequently the groups were then split into “training” and “test” groups. On the basis of the training group, it was then possible to identify 21 metabolites that significantly differed according to type 2 diabetes status. Using machine learning approaches and decision tree modeling, the authors report that it was possible to predict type 2 diabetes incidence with 83% accuracy in the training group and 77% in the test group. According to the authors, these outcomes were far superior to the outcomes predicted by testing plasma glucose alone. The risk of GDM turning into type 2 diabetes can be high following pregnancy. Detecting this risk in individuals usually relies on the patient undergoing a 2-h oral glucose tolerance test, as recommended by the American Diabetes Association. However according to the authors, screening rates are low, possibly due to the sheer inconvenience of the test, which they suggest can be overcome by detecting metabolomics signatures in blood samples.

Allalou et al. A predictive metabolic signature for the transition from gestational diabetes mellitus to type 2 diabetes. Diabetes 2016;65:2529–2539

DOI: 10.2337/db16-ti09