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In This Issue of *Diabetes*

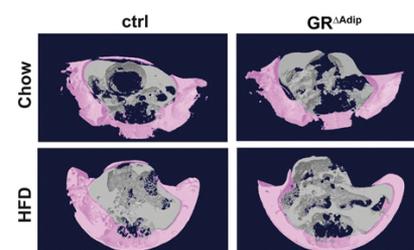
By Max Bingham, PhD

Glucocorticoid Receptors in Adipose Tissue: Key to Energy Metabolism?

Mueller et al. (p. 272) studied the role of the glucocorticoid receptors in adipose tissue, revealing a central role for the receptor in controlling energy metabolism and partitioning of nutrients during times of fasting and feeding. Involving a mouse model with the gene for the receptor knocked out only in adipocytes and controls, the study used metabolomics and a series of biological and molecular techniques to pick apart how much of an impact the receptor likely has on global metabolism. The authors report considerable changes in circulating metabolites relating to lipid metabolism or amino acid metabolism and reduced lipolytic and gluconeogenic capacity in the mice lacking the receptor genes. Furthermore, exposing these mice to cold reportedly resulted in reduced thermogenesis capacity, again supporting impaired lipolytic function. Subsequent molecular analyses suggested that the receptor knockout was likely responsible for the impaired signal transduction from β -adrenergic receptors to adenylate cyclase and the normal activation of the lipolytic cascade in adipose tissue. They report further that diet-induced or aging-associated obesity was reduced and the development of liver steatosis and deterioration of glucose metabolism was attenuated in mice with no glucocorticoid receptors. Taken together, the results suggest that the glucocorticoid receptor in adipocytes likely exerts central but diverging roles in metabolic homeostasis that are dependent on energetic state and, in certain circumstances, might promote adiposity and associated disorders. Commenting more widely on the study, authors Richard Moriggl and Jan P. Tuckermann told *Diabetes*: "Apart from underlining that systemic energy metabolism, at least in part, is controlled centrally via the adipocyte glucocorticoid receptor, our studies suggest that inhibition of the glucocorticoid pathway in adipose tissue may lead to conditions which prevent the gain of fat mass in a metabolically harmful manner. Age- and malnutrition-associated diseases like obesity can promote serious diseases such as liver cancer or cardiovascular disease. If we can better define the role of glucocorticoids in adipose tissue under these conditions, we might be able to identify new strategies to counteract obesity-related complications. Future studies to reveal underlying mechanisms and potential therapeutic implication are thus warranted."

Oxytocin and Metabolic Regulation of Glucose Homeostasis: Data From Human Study

A systematic investigation of the role of oxytocin in metabolic regulation and glucose homeostasis suggests it may play a significant role in glucose metabolism and β -cell function and should now be considered a candidate for broader investigations in a clinical context. The study by Klement et al. (p. 264) assessed the effect of intranasally administered oxytocin versus placebo in 29 healthy male subjects who underwent oral glucose tolerance tests. The design involved a double-blind crossover comparison with blood samples collected for a range of parameters, including glucose, insulin, and glucagon, among many others. Insulin sensitivity and β -cell function was then assessed according to the oral minimal model method. According to the authors, oxytocin attenuated peak excursions of both plasma glucose and C-peptide and resulted in a more rapid increase of insulin and C-peptide in comparison to the control condition of the experiment. The oral minimal model analyses indicated that β -cell responsiveness was enhanced in comparison to the control condition and that this was driven almost entirely by an enhanced dynamic response. There was also a twofold increase in glucose tolerance as indicated by the disposition index. No or minimal effects on other biochemical parameters (e.g., cortisol, lactate, and nonesterified fatty acids, among others) are reported. On the basis of the data and other fairly recent studies, the authors suggest oxytocin should now be considered for testing in a clinical context and that it might be particularly effective for postprandial hyperglycemia in type 2 diabetes. Author Johanna Klement said: "The results of our recent study underline that the intranasal administration of peptides like oxytocin can elucidate metabolic effects of centrally acting hormones in humans that deserve closer attention. Our findings of oxytocin's effects on glucose regulation in men are promising, but also call for a closer look at its impact in a broader context, such as investigations that address potential interactions of oxytocin with gender, BMI, and diabetes mellitus."



Adipocyte-specific glucocorticoid receptor (GR)-deficient mice gain less weight under high-fat diet (HFD) conditions. Three-dimensional models of subcutaneous (pink) and visceral (gray) fat in the abdominal region of mice fed a chow diet or HFD. ctrl, control.

Mueller et al. Adipocyte glucocorticoid receptor deficiency attenuates aging- and HFD-induced obesity and impairs the feeding-fasting transition. *Diabetes* 2017;66:272–286

Klement et al. Oxytocin improves β -cell responsiveness and glucose tolerance in healthy men. *Diabetes* 2017;66:264–271

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Follicular T Helper Cells Are Increased Close to Diagnosis of Type 1 Diabetes: A Clue to Prevent Progression of the Disease?

A comprehensive characterization of T helper cells and B cells in children at risk of type 1 diabetes has revealed that a particular type of circulating T helper cell is increased in certain circumstances around the time of diagnosis of the disease. According to Viisanen et al. (p. 437), the outcome raises the possibility of targeting the cells with immune therapies to potentially prevent the progression to type 1 diabetes. The study used samples from the Finnish Type 1 Diabetes Prediction and Prevention Project (DIPP) follow-up study, focusing on 54 children with type 1 diabetes, 58 at-risk children positive for multiple autoantibodies, 15 at-risk children with impaired glucose control, and 149 control subjects. Then, using blood samples collected over 30 months and flow cytometric analyses, the authors report a comprehensive survey of T cells, B cells, and interleukin-21 to characterize their roles in disease progression. According to the authors, the striking finding was that the frequency of activated follicular T helper cells was increased in children with newly diagnosed type 1 diabetes and in at-risk children with impaired glucose tolerance. However, this increase was only evident when the children were positive for two or more autoantibodies. It is this finding they say that provides direct evidence for a role of follicular T helper cells in the progression of the disease and that specifically for children with multiple autoantibodies there may be real opportunities to therapeutically target the cells to prevent progression of the disease. Commenting more widely on the study, Tuure Kinnunen said: "Together with recent results by other research groups our findings suggest that follicular T helper cells may have a role in the pathogenesis of type 1 diabetes and could therefore provide an attractive target for immunotherapeutic intervention. Moreover, our results lend support to the idea that different disease endotypes, i.e., disease subgroups with distinct pathological mechanisms, exist in type 1 diabetes and that these could be distinguished based on the pattern of autoantibodies detected in the blood samples of patients."

Viisanen et al. Circulating CXCR5+PD-1+ICOS+ follicular T helper cells are increased close to the diagnosis of type 1 diabetes in children with multiple autoantibodies. *Diabetes* 2017;66:437–447

Increase in Systolic Blood Pressure Due to Genetic Variants Also Increases Type 2 Diabetes Risk: Meta-analysis

Increases in systolic blood pressure are associated with future onset of type 2 diabetes, but whether this relationship is causal or simply a correlation has remained an open question due to the difficulties of investigating such relationships. According to Aikens et al. (p. 543), genetically elevated systolic blood pressure also increases risk for type 2 diabetes and, as a consequence, indicates the likely existence of pathways and mechanisms that can be targeted therapeutically. Their study relies on a technique called the Mendelian randomization framework and uses known relationships between 28 genetic variants with small effects on levels of systolic blood pressure to then evaluate their impact on type 2 diabetes. On the basis of data from thousands of individuals, the authors report that elevation of systolic blood pressure due to genetic variation by 1 mmHg resulted in a 2% increase in risk of type 2 diabetes, compatible with observed correlations from previous epidemiological studies. The framework exploits natural randomization of genotypes in the study population to help address reverse causality and confounding by selecting genetic variants that exclusively associate with systolic blood pressure. Combining multiple variants into a genetic risk score can then enable a test of the hypothesis that elevations in blood pressure directly increases the risk of type 2 diabetes. According to the authors, their result was robust following a much more conservative analysis using 13 genetic variants and remained so after multiple sensitivity analyses that used alternative measures and simulation studies. They go on to speculate (carefully) about possible underlying mechanisms, though they state that further work will be required to understand the physiological basis for the observed effect. Author Benjamin F. Voight said: "Causal inference is undoubtedly a very challenging problem in biology and medicine. Because the relationship between blood pressure and diabetes is quite complex, we are optimistic that human genetics data will continue to provide flashes of insight, ultimately leading to new therapeutic indications."

Aikens et al. Systolic blood pressure and risk of type 2 diabetes: a Mendelian randomization study. *Diabetes* 2017;66:543–550

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