JULY 2015

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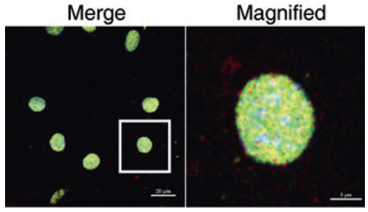
In This Issue of *Diabetes*

By Max Bingham, PhD

Obesity Induced by Diet Is Prevented by Endostatin: New Mouse and In Vitro Data

Mice fed a high-fat (60% fat) diet plus endostatin did not become obese or develop the equivalent obesity-related diabetic complications at the same rate as mice given the same diet minus endostatin. That is the conclusion of Wang et al. in a study reported in this issue of *Diabetes* (**p. 2442**). Following up the animal studies, the researchers also detail relevant cell line studies that uncover specific mechanisms and cellular targets that endostatin might influence. Most importantly, the data point toward endostatin inhibiting both adipogenesis and angiogenesis and that together those processes might also have an antiobesity effect that is modified via endostatin. The mechanisms detailed in the report suggest that endostatin first interacts with the protein Sam68 in the nuclei of preadipocytes. This interaction appears to then competitively impair binding of the protein to mTOR (mechanistic/mammalian target of rapamycin), which ultimately leads to transcription errors and defects in adipogenesis. The biological and clinical significance of these outcomes appear to be clear, according to author Dr. Yongzhang Luo, from Tsinghua University, Beijing, China: "Our data suggest that endostatin indirectly prevents adipogenesis by inhibiting angiogenic capacity of endothelial cells. Thus, endostatin may be an important mediator of the white adipose tissue microenvironment and obesity-related diabetic complications, which need to be investigated in the future. These findings provide new insights into the biological relevance of this protein. We have also demonstrated that endostatin inhibits dietary-induced obesity and its related metabolic disorders. Although clinical trials of endostatin as an antitumor drug are not a good model to determine the effect of endostatin on body weight because of the combined use of endostatin and chemo drugs, it has been proven that endostatin is safe with rare untoward reactions or side effects and no drug resistance in these human clinical trials. Thus, endostatin has a great potential to be employed in antiobesity therapy and the prevention of obesity-related diabetic complications."



Endostatin colocalizes with Sam68 intracellularly in 3T3-L1s.

Wang et al. Endostatin prevents dietary-induced obesity by inhibiting adipogenesis and angiogenesis. Diabetes 2015;64:2442–2456

Evidence of Direct Vasodilation Effects of Exenatide in Type 2 Diabetes: Clinical, Mechanistic Data

Two clinical studies in a report in this issue of *Diabetes* (**p. 2624**) add to the evidence that exenatide, a GLP-1 receptor (GLP-1R) agonist, can improve endothelial function and inhibit postmeal increases of glucose and triglyceride concentrations in patients with type 2 diabetes. The report by Koska et al. suggests that exenatide may directly affect vasodilation and improved endothelial function independent of reductions in plasma triglycerides and glucose. Exendin-9, a GLP-1R antagonist, is reported in one of the trials to blunt the effects of exenatide on vasodilation, strengthening the evidence for a direct association. To investigate the molecular mechanisms of these effects, the authors further report a series of ex vivo experiments on human arterioles and endothelial cells. In short, exenatide appears to activate endothelial nitric oxide synthase (eNOS) and to increase nitric oxide production in endothelial cells, again suggesting direct effects on vasodilation. Separately, exenatide also induced vasorelaxation and reduced endothelial dysfunction in arterioles ex vivo in the presence of high levels of glucose and lipids. Both sets of effects were reduced when AMPK was inhibited. AMPK activation appeared to precede activation of eNOS in the experiments, thereby confirming a role. Taken together, the data suggest a direct effect of exenatide on GLP-1R and AMPK activation that results in improved endothelial function. As endothelial dysfunction is important in the progression of atherosclerosis and a variety of other cardiovascular diseases, the use of exenatide, and presumably GLP-1R agonists in general, could be important for managing the progression of type 2 diabetes and its complications. Specifically, this study provides conceptual and mechanistic support for their potential use in cardiovascular disease protection in type 2 diabetes. Testing in appropriately powered clinical studies will be important steps for exenatide in diabetes.

Koska et al. Exenatide protects against glucose- and lipid-induced endothelial dysfunction: evidence for direct vasodilation effect of GLP-1 receptor agonists in humans. Diabetes 2015;64:2624–2635

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Vascular Outcomes Worsen Following Repeated Hypoglycemia in Healthy Adults

In another trial published in this issue of *Diabetes* (**p. 2571**), the effects of repeated episodes of hypoglycemia on a variety of vascular biomarkers, mechanisms, and endothelial function in healthy individuals have been revealed for the first time. Repeated episodes of hypoglycemia can result in serious adverse cardiovascular events. This is particularly the case in type 2 diabetes where standard and intensive treatment of patients can (unintentionally) result in episodes of severe hypoglycemia. Surprisingly little is known about the mechanisms that kick in following repeated episodes of hypoglycemia. In light of recent trial evidence that showed individuals with high HbA_{1c} tended to suffer worse cardiovascular outcomes following severe hypoglycemia, the outcome of this study could well inform future clinical practice in terms of the management of type 2 diabetes. Specifically, Joy et al. report that a moderate episode of hypoglycemia results in increases in a variety of proinflammatory and coagulation biomarkers, impairment of fibrinolytic balance, platelet activation, and reduced nitric oxide–mediated endothelial function. Repeated episodes further impair endothelial function and considerably alter the dynamics of a variety of other vascular markers. Commenting on the overall result, the authors are clear on the effects of repeated episodes of hypoglycemia: "The results of the current study clearly demonstrate that despite reduced neuroendocrine and autonomic nervous system counterregulatory responses, repeated hypoglycemia produces a greater aggregate of deleterious in vivo vascular biologic effects compared with a single similar hypoglycemic episode." While the study was performed in healthy subjects, it does provide evidence of the clear effects of repeated episodes of hypoglycemia and that these pose risks in terms of cardiovascular health. As patients with diabetes are already at a higher risk of hypoglycemic episodes, the study underlines the importance of good glycemic control to avoid more serious complications later.

Joy et al. Effects of acute and antecedent hypoglycemia on endothelial function and markers of atherothrombotic balance in healthy humans. Diabetes 2015;64:2571–2580

GLP-1 Response in Prediabetes and Type 2 Diabetes Is Reduced by Up to 25%

GLP-1 response to oral glucose intake is lower in individuals with prediabetes or type 2 diabetes by between 16 and 25% in comparison to individuals with normal glucose tolerance. This is according to the outcomes of the largest ever clinical investigation into GLP-1 secretion following glucose intake in humans. The study is reported in this issue of *Diabetes* (**p. 2513**). The GLP-1 response was 25% lower in comparison to control subjects, particularly in women with prediabetes. GLP-1 is a potent antihyperglycemic gut hormone that induces glucose-dependent stimulation of insulin secretion and therefore is essential in maintaining plasma glucose concentrations within normal ranges. The report by Færch et al. details the outcomes of the ADDITION-PRO study, a longitudinal risk-stratified cohort study based in Denmark of individuals at low to high risk of developing type 2 diabetes. The study involved 1,462 adults comprising individuals with normal glucose tolerance, prediabetes, or type 2 diabetes. Notable other outcomes of the study include obese and overweight individuals having a 20% reduced GLP-1 response in comparison to individuals of normal weight—and this was independent of glucose tolerance status. The conclusions of the authors are clear: "Our findings indicate that a reduction in GLP-1 response to oral glucose occurs prior to the development of type 2 diabetes and obesity, which can have consequences for early prevention strategies for diabetes." More specifically, the authors indicate that "treatment with GLP-1 analogs could be relevant as part of a prevention strategy if weight loss attempts are unsuccessful…." Commenting on the wider implications of the study, lead author Dr. Kristine Færch told us: "The study contributes to a better understanding of the pathophysiology of type 2 diabetes, and seen from a primary prevention perspective, the results are highly interesting and encouraging. However, results from randomized controlled trials investigating whether treatment with GLP-1 analogs can prevent or delay the onset of type 2 diabetes in high-risk individuals are needed before we can conclude whether GLP-1 should be used in the prevention of type 2 diabetes."

Færch et al. GLP-1 response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes, and obesity and influenced by sex: the ADDITION-PRO study. Diabetes 2015;64:2513–2525

DOI: 10.2337/db15-ti07