

Highlights From the Latest in Diabetes Research

Adipocyte-Specific Circadian Control of Appetite and Feeding Behavior

Adipocytes play multiple roles in energy balance: they store and release energy and also provide signals to the CNS about energy storage. One example of the importance of white adipose tissue in energy balance involves release of fatty acids into the circulation. When this occurs, fatty acid concentrations increase in the hypothalamus—a change that results in signals that decrease food intake. Growing interest in circadian control of the systems underpinning appetite and feeding led to the observation that mice with germline knockout of *Arntl* (a gene encoding a key molecular clock element) are heavier and have more adipose tissue than their wild-type counterparts and that these differences become evident as early as 4–8 weeks. A new report by Paschos et al. takes this line of investigation further by determining the impact on weight and food intake when *Arntl* is specifically deleted from adipocytes. The investigators demonstrate that in contrast to mice in which *Arntl* is deleted in hepatocytes of β -cells, loss of *Arntl* in adipocytes led to marked disruption of circadian oscillation of circulating free fatty acids. Although mice lacking adipocyte *Arntl* were born with the same weight as their wild-type counterparts, mutant mice were significantly heavier at 9 weeks. This occurs because *Arntl* regulates the circadian release of polyunsaturated fatty acids, which act on the hypothalamus to regulate feeding behavior. Specifically, increased hypothalamic levels of unesterified polyunsaturated free fatty acids, as occurs during the day, inhibit feeding behavior in mice. Thus, absence of *Arntl* leads to lower circulating and hypothalamic concentrations of polyunsaturated fatty acids during the daytime, leading to increased food intake. Their study also indicated that even in settings where the total number of calories was held constant, mutant mice that were fed a high-fat diet and whose feeding was restricted to the light period gained more weight than their counterparts that were fed during the dark period. The investigators then showed that relative to controls, mice lacking adipocyte *Arntl* had higher expression of neuropeptide Y and agouti-related peptide (both appetite-inducing) during the light cycle and lower levels of cocaine- and amphetamine-regulated transcript, which would inhibit appetite and increase thermogenesis. Consistent with increased weight, mutant mice also had higher circulating concentrations of triglycerides and saturated fatty acids. In contrast, they had lower circulating concentrations of unsaturated fatty acids, which were associated with lower fatty acid levels in the hypothalamus that may in turn increase food intake. These intriguing results show that the intrinsic circadian clock in adipocytes regulates food intake by

modulating circadian release of polyunsaturated fatty acids that influence hypothalamic regulation of appetite. — Helaine E. Resnick, PhD, MPH

- Paschos et al. Obesity in mice with adipocyte-specific deletion of clock component *Arntl*. *Nat Med* 2012;18:1768–1777

Obesity and Mortality: Big Numbers Do Not Lie

Accepted categories of BMI define normal weight as BMI of 18.5 to <25 kg/m², overweight as BMI 25 to <30 kg/m², and obesity as BMI \geq 30 kg/m². Among obese individuals, grade 1 obesity is defined as BMI 30 to <35 kg/m² and grades 2 and 3 obesity include BMI \geq 35 kg/m². This categorization scheme underpins public health priorities and benchmarking activities in the U.S. and elsewhere and suggests that unfavorable health outcomes should be observed at BMI exceeding 25 kg/m². A new meta-analysis of 97 studies indicates that rethinking of the relationship between these categories and mortality—arguably the most unfavorable health outcome related to obesity—might be in order. This report, which pooled data for more than 2.88 million individuals, examined over 270,000 deaths in relation to accepted BMI categories. Results from this ambitious effort showed that relative to those with normal weight, overweight individuals—those with BMI 25 to <30 kg/m²—had a significantly lower risk of death (hazard ratio [HR] 0.94 [95% CI 0.91–0.96]). In contrast, the HR for the pooled group of obese individuals (grades 1–3 combined) was elevated relative to normal weight (HR 1.18 [1.12–1.25]). However, mortality among people with grade 1 obesity was lower but did not differ statistically relative to people with normal weight (HR 0.95 [0.88–1.01]), whereas those with grades 2 and 3 obesity experienced higher mortality relative to people with normal weight (HR 1.29 [1.18–1.41]). These findings concur with earlier research suggesting lower mortality among overweight individuals and those with moderate obesity. The authors propose a number of possible explanations for these results, including issues related to earlier and more optimal receipt of medical care among overweight individuals, as well as potentially favorable biological effects associated with greater fat levels or higher metabolic reserves. Although there is evidence to suggest that obesity is associated with elevated morbidity, disability, and health care costs, higher mortality does not appear to be on the list of outcomes related to being overweight as it is currently defined. — Helaine E. Resnick, PhD, MPH

- Flegal et al. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013;309:71–82

Pancreatic Deletion of PPAR β/δ Improves β -Cell Mass and Function in Mice

Although it is generally accepted that PPAR β/δ has favorable effects on obesity through actions in muscle, fat, and liver, its role in the pancreas is less well understood. In a new report by Iglesias et al., data from mice lacking pancreatic PPAR β/δ shed new light on the role of this fatty acid sensing nuclear receptor in the pancreas. Relative to their wild-type counterparts, mice lacking PPAR β/δ in the pancreas had higher insulin and lower glucose levels starting at 4 weeks of age. At 8 weeks of age, the mutant mice also had more favorable responses to glucose tolerance testing compared with controls, and their insulin responses were more pronounced. In contrast, glucose clearance was similar among mice lacking pancreatic PPAR β/δ and controls. Although additional experiments exploring the relationship between PPAR β/δ deletion and β -cell mass showed no differences in endocrine precursor or insulin-expressing cells in embryonic mice, 8-week-old mutant mice had twice the β -cell mass as did controls—a difference that was due to increased numbers of islets. Interestingly, pancreatic α -cells also increased among PPAR β/δ -deficient mice, but glucagon levels did not change in the islets or pancreas. In experiments designed to explore the impact of the enhanced β -cell mass on β -cell function among mutant mice, investigators observed enhanced second-phase insulin responses relative to controls in the setting of elevated (16.7 mmol/L) glucose. In contrast, insulin secretion was similar between the groups at basal glucose levels as well as during the first-phase insulin response in elevated glucose. This new report yields intriguing data supporting new roles for PPAR β/δ and raises the possibility that these mechanisms could be manipulated in a tissue-specific manner to promote β -cell survival and insulin secretion in the setting of type 2 diabetes. — Helaine E. Resnick, PhD, MPH

- Iglesias et al. PPAR β/δ affects pancreatic β cell mass and insulin secretion in mice. *J Clin Invest* 2012;122:4105–4117

Pancreatic Atrophy: A Subclinical Indicator of Type 1 Diabetes?

Although identifying individuals at risk for type 1 diabetes may offer opportunities to intervene prior to disease onset, reliable strategies to achieve this goal remain elusive. New data from the Network for Pancreatic Organ Donors with Diabetes program (a group that collaborates with organizations that procure organs for transplantation and research) offer insight into a potentially novel approach for risk stratification for type 1 diabetes in apparently healthy individuals. Prior to organ harvest, screening for GAD antibodies and insulinoma-associated 2ic was conducted. This information was examined with post-harvest data on insulin autoantibodies and zinc transporter 8 antigens. Presence of type 1 diabetes was defined based on laboratory determinations and chart review. The newly published data summarize findings from three groups: 23 control subjects, 8 individuals without type 1 diabetes who were positive for single islet autoantibodies, and 20 individuals with type 1 diabetes. With the exception of diabetes-related factors, clinical characteristics were similar across these groups. However, there was a pattern reflecting a significant, stepwise decrease in pancreatic weight across the three groups that was consistent with the idea of increasing pancreatic atrophy with advancing type 1 diabetes pathology. Mean pancreatic weight for control subjects was 81.4 g, and it decreased to 61.3 g in the single autoantibody group and diminished further to 44.9 g in the type 1 diabetic group. The authors acknowledge the relatively small sample size in this study, but point out that atrophy of the pancreas may be an early, subclinical feature of type 1 diabetes. If this is the case, exploration of the potential role of pancreatic atrophy in the evolution of type 1 diabetes might prove valuable, as well as examination of the potential use of pancreatic weight in type 1 diabetes risk assessment and stratification. — Helaine E. Resnick, PhD, MPH

- Campbell-Thompson et al. Pancreas organ weight in individuals with disease-associated autoantibodies at risk for type 1 diabetes. *JAMA* 2012;308:2337–2339

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