Boston Obesity Nutrition Research Center
Start Date: 1992
Status: Ongoing
Source of NIH Support: NIDDK
Website: www.bmc.org/bonrc

Organization and Goals

The Boston Obesity Nutrition Research Center (BONRC), based at the Boston Medical Center since October 1998, represents a collaborative effort of five major Boston institutions that represent all three medical schools in the city. These include the Tufts-New England Medical Center (Tufts University), Massachusetts General Hospital (Harvard University), Beth Israel Deaconess Medical Center (Harvard University), Boston Medical Center (Boston University), and Harvard School of Public Health (Harvard University). BONRC goals are to:

- Foster ongoing collaborative relationships among healthcare professionals and scientists interested in the study of obesity and nutrition;
- Produce the major advances necessary to resolve the questions surrounding the development of obesity and the regulation of energy metabolism; and
- Promote interactions among scientists and institutions and make resources available through support of pilot and feasibility studies, an enrichment program, and the core laboratories.

BONRC activities focus on three major themes: the natural history of obesity, energy metabolism in health and disease, and education and training.

Core Laboratories

Administrative Core (Boston Medical Center): Barbara E. Corkey, Ph.D., Director; George L. Blackburn, M.D., Ph.D., Associate Director

External Advisory Group Members:
Eugenia E. Calle, Ph.D., American Cancer Society (09/05-08/08)
Susan K. Fried, Ph.D., University of Maryland (09/05-08/08)
Craig Hanis, Ph.D., The University of Texas Health Science Center at Houston (09/04 – 08/07)
Steven B. Heymsfield, M.D., Merck Research Laboratories (03/04-02/07)

Adipocyte Core (Boston Medical Center): **James Kirkland, M.D., M.Sc., Ph.D., Director**

Epidemiology and Biostatistics Core (Harvard School of Public Health): Graham Colditz, M.D., Dr.P.H., Director (thru 10/03); Frank B. Hu, M.D., M.P.H., Ph.D., Director (11/03-present)

Human Metabolic and Genetic Core (Tufts-New England Medical Center): Ernst Schaefer, M.D., Director

Transgenic Core (Beth Israel Deaconess Medical Center): Bradford Lowell, M.D., Ph.D., Director

Pilot and Feasibility Studies

Assessing the Physiological Function of Melanocortin-4-Receptors (MC4R) in Specific Brain Areas Using a Re-Activatable MC4R Null Allele. Nina Balthasar, Ph.D., Beth Israel Deaconess Medical Center. The aim of this project is to identify key neuronal sites mediating the "anti-obesity and anti-diabetes" actions of MC4Rs.

The Role of Insulin-Degrading Enzyme in Obesity and Metabolism. R. Wesley Farris, II, M.D., Brigham and Women's Hospital. The goal of this project is to assess the *in vivo* and cellular role of IDE in regulating insulin levels and body weight.

Regulation of Adipose Triglyceride Lipase (ATGL) by Insulin, TNFα, and PPARγ. Erin Kershaw, M.D., Beth Israel Deaconess Medical Center. This project will test the hypothesis that the effects of insulin, TNFα, and PPARγ on lipolysis are mediated, at least in part, via regulation of ATGL.

Phosphofructokinase-M and Adipose Mass. Keith Tornheim, Ph.D., Boston University School of Medicine. This project is based on the observation of decreased fat in mice deficient in the M-isoform of phosphofructokinase (PFK-M).

Role of BMPs on Determination of Brown vs. White Adipocyte Differentiation. Yu-Hua Tseng, Ph.D., Joslin Diabetes Center. The goals of this project are to elucidate the molecular mechanisms by which BMPs influence adipocyte cell date decision and regulate balance in both in vitro and *in vivo* settings.

Studies on Retinaldehyde Functions in Adipogenesis. Ouliana Ziouzenkova, Ph.D., Brigham and Women's Hospital. This project will test the hypothesis that Rald inhibits adipogenesis through the mechanism including suppression of PPARγ and RXRα transcriptional responses.

Effect of Medium Chain Triglycerides on Body Composition, Glycemic Control and Adipokine Production in Obese Type 2 Diabetics. Caroline Apovian, M.D., Boston Medical Center. The specific aims of this project are to determine whether 1) MCT is more efficient in decreasing fat mass while retaining lean mass than LCT and how this correlates with improved clinical outcomes in obese diabetics and 2) MCT might lead to altered adipocyte morphology and adipokine profiles to improve insulin sensitivity in obese diabetics.

Changes in GIP Expression and Insulin Sensitivity Following Laparoscopic Roux-en-Y Gastric Bypass vs. Laparoscopic Adjustable Gastric Band. Marie McDonnell, M.D., Boston Medical Center. This study will serve to characterize the enteroinsular axis in obese subjects with impaired glucose tolerance.

Effects of Caffeinated and Decaffeinated Coffee on Body Weight and Glucose Tolerance. Rob van Dam, Ph.D., Harvard School of Public Health. This project will study the effects of caffeinated and decaffeinated coffee consumption on body fatness, insulin sensitivity, and glucose tolerance that may underlie the observed associations with a lower risk of type 2 diabetes in a randomized controlled trial.

Funding Derived From Previous Pilot and Feasibility Studies

Identification of Central Targets of Ghrelin. Jeffrey Zigman, M.D., Ph.D., University of Texas Southwestern Medical Center. Funding: ADA, 1/1/2006-02/28/2008.

Characterization of GIP Signaling in Adipocytes. Diane Song, Ph.D., Boston Medical Center. Funding: NIH/NIDDK 1F32DK067812-01A1, 02/15/2005-02/14/2008.

Roles of PTP1B in Insulin and Leptin Action *In Vivo*. Janice Zabolotny, Beth Israel Deaconess Medical Center. Funding: NIH/NIDDK, 09/01/2005-08/31/2007.

Roles of PTP 1B Overexpression in Pathogenesis *In Vivo*. Janice Zabolotny, Beth Israel Deaconess Medical Center. Funding: NIH/NIDDK, 09/30/2005-08/31/2007.

Scientific Advances/Accomplishments

Progress is reflected in the manuscripts that were published using facilities from the various Cores. Following is a summary of some of the highlights in each Core during this period.

Adipocyte Core

Dynamics of Lipid Droplet Associated Proteins During Hormonally Stimulated Lipolysis in Engineered Adipocytes: Stabilization and Lipid Droplet Binding of ADRP/Adipophilin. *Mol. Endo.* (in press) Gross DN, Miyoshi H, Hosaka T, Zhang HH, Pino E, Souza S, Obin M, Greenberg AS, Pilch PF. In mature adipocytes, triglyceride is stored within lipid droplets, which are coated with the protein perilipin, which functions to regulate lipolysis by controlling lipase access to the droplet in a hormone-regulatable fashion. Adipocyte-differentiation related protein (ADRP) is a widely expressed lipid droplet binding protein that is co-expressed with perilipin in differentiating fat cells, but is minimally present in fully differentiated cultured adipocytes. We find that fibroblasts ectopically expressing C/EBPalpha (NIH-C/EBPalpha cells) differentiate into mature adipocytes that simultaneously express perilipin and ADRP proteins. In response to isoproterenol, perilipin is hyper-phosphorylated and lipolysis is enhanced, and subsequently, ADRP protein expression increases coincident with its surrounding intracellular lipid droplets. In the absence of lipolytic stimulation, inhibition of proteasomal activity with MG-132 increased ADRP levels to those of cells treated with 10 microM isoproterenol, but ADRP does not surround the lipid droplet in the absence of lipolytic stimulation. We overexpressed a perilipin A construct in NIH-C/EBPalpha cells where the six serine residues known to be phosphorylated by PKA were changed to alanine (Peri A Delta1-6). These cells show no increase in ADRP expression in response to isoproterenol. We propose that ADRP can replace perilipin on existing lipid droplets or those newly formed as a result of fatty acid re-esterification, under dynamic conditions of hormonally stimulated lipolysis, thus preserving lipid droplet morphology/structure.

Eicosapentaenoic Acid, but not Oleic Acid, Stimulates β-oxidation in Adipocytes. *Lipids* 40: 815-21, 2005. Guo W, Xie W, Lei T, Hamilton JA. The beneficial roles of dietary fish oil in lowering serum TAG levels in animals and humans have been attributed in part to the high content of two n-3 polyunsaturated very long-chain FA, EPA, and DHA. Recent studies show that EPA induces mitochondrial beta-oxidation in hepatocytes, which might contribute to the systemic lipid-lowering effect. Whether EPA affects FA storage or oxidation in adipocytes is not

clear. To investigate this possibility, 3T3-L1 adipocytes incubated with EPA (100 microM) for 24 hours were assayed for beta-oxidation, carnitine palmitoyl transferase 1 (CPT-1) activity, protein, and mRNA expression of CPT-1. For comparison, cells treated with oleic acid, octanoic acid, and clofibrate, a synthetic ligand for peroxisome proliferator-activated receptor alpha were also analyzed. Mitochondria were isolated by differential centrifugation, and the mitochondrial membrane acyl chain composition was measured by GLC. EPA increased the oxidation of endogenous FA but did not inhibit lipogenesis. Oleic acid and clofibrate did not affect FA oxidation or lipogenesis, whereas octanoic acid suppressed the oxidation of endogenous FA and inhibited lipogenesis. Increased beta-oxidation by EPA was associated with increased CPT-1 activity but without changes in its mRNA and protein expression. EPA treatment increased the percentage of this FA in the mitochondrial membrane lipids. We suggest that EPA increased the activity of CPT-1 and beta-oxidation in adipocytes by altering the structure or dynamics of the mitochondrial membranes.

Abundance of Two Human Preadipocyte Subtypes With Distinct Capacities for Replication, Adipogenesis, and Apoptosis Varies Among Fat Depots. *Am. J. Physiol.* 288:E267-E277, 2005. Tchkonia T, Tchoukalova Y, Giorgadze N, Pirtskhalava T, Karagiannides I, Forse RA, Koo A, Stevenson M, Chinnappan D, Cartwright A, Jensen MD, Kirkland JL. Fat depots vary in function and size. The preadipocytes that fat cells develop from exhibit distinct regional characteristics that persist in culture. Human abdominal subcutaneous cultured preadipocytes undergo more extensive lipid accumulation, higher adipogenic transcription factor expression, and less TNF-alpha-induced apoptosis than omental preadipocytes. We found higher replicative potential in subcutaneous and mesenteric than in omental preadipocytes. In studies of colonies arising from single preadipocytes, two preadipocyte subtypes were found, one capable of more extensive replication, differentiation, and adipogenic transcription factor expression and less apoptosis in response to TNF-alpha than the other. The former was more abundant in subcutaneous and mesenteric than in omental preadipocyte populations, potentially contributing to regional variation in replication, differentiation, and apoptosis. Both subtypes were found in strains derived from single human preadipocytes stably expressing telomerase, confirming that both subtypes are of preadipocyte lineage. After subcloning of cells of either subtype, both subtypes were found, indicating that switching can occur between subtypes. Thus proportions of preadipocyte subtypes with distinct cell-dynamic properties vary among depots, potentially permitting tissue plasticity through subtype selection during development. Furthermore, mesenteric preadipocyte cell-dynamic characteristics are distinct from omental cells, indicating that visceral fat depots are not functionally uniform.

Epidemiology Core

The Impact of a School-based Obesity Prevention Trial on Disordered Weight Control Behaviors in Early Adolescent Girls. *Arch Pediatr Adolesc Med* 2005;159(3):225-230. Austin SB, Field AE, Wiecha J, Peterson KE, Gortmaker SL. The objective of this study is to assess the impact of an obesity prevention intervention on use of self-induced vomiting/laxatives (purging) and diet pills to control weight in girls in early adolescence. We matched and randomly assigned 10 middle schools to an intervention or a control condition in a randomized controlled trial. Longitudinal multivariable analyses using generalized estimating equations were conducted with data from 480 girls to examine the effects of the intervention on the risk of reporting a new case of purging or diet pill use to control weight at follow up 21 months later, while controlling for ethnicity and school matched pairs. Girls who reported purging or using diet pills at baseline were excluded from analyses. Four hundred eighty girls in early adolescence aged 10 to 14 years

(mean age, 11.5 years) participated. The Planet Health obesity prevention program was implemented during 2 school years and was designed to promote healthful nutrition and physical activity and to reduce television viewing. Reduced risk of using self-induced vomiting/laxatives or diet pills to control weight in the past 30 days was the outcome. After the intervention, we found 14 (6.2 percent) of 226 girls in control schools and 7 (2.8 percent) of 254 girls in intervention schools reported purging or using diet pills to control their weight (P = .003). In a multivariable generalized estimating equation model, girls in intervention schools were less than half as likely to report purging or using diet pills at follow-up compared with girls in control schools (odds ratio, 0.41; 95 percent confidence interval, 0.22-0.75). These findings provide promising evidence that school-based interventions may effectively integrate prevention of both obesity and disordered weight-control behaviors.

The Association of Fried Food Consumption Away From Home With Body Mass Index and Diet Quality in Older Children and Adolescents. *Pediatrics* 2005;116(4):e518-24. Taveras EM, Berkey CS, Rifas-Shiman SL, Ludwig DS, Rockett HRH, Field AE, Colditz GA, Gillman MW. Rates of overweight have increased dramatically among children in the United States. Although an increase in consumption of food prepared away from home has paralleled overweight trends, few data exist relating food prepared away from home to change in BMI in children. The goals of this study were to: examine the cross-sectional and longitudinal associations between consumption of fried foods away from home (FFA) and BMI and examine the cross-sectional associations between intake of FFA and several measures of diet quality. We studied a cohort of 7,745 girls and 6,610 boys, aged 9 to 14 years, at baseline in 1996. We obtained BMI from self-reported height and weight, measures of diet quality from a food frequency questionnaire, and weekly servings of FFA during the previous year. We performed linear regression analyses to assess the longitudinal associations between changes in consumption of FFA on change in BMI, using data from three 1-year periods from 1996 through 1999. We also related consumption of FFA with intake of selected foods and nutrients at baseline. In cross-sectional analyses, adjusting for potential confounders, mean (SE) BMI was 19.1 (0.13) among children who ate FFA "never or <1/week," 19.2 (0.13) among those who responded "1 to 3 times/week," and 19.3 (0.18) among those who responded "4 to 7 times/week." In longitudinal multivariate models, increasing (over 1 year) consumption of FFA "never or <1/week" to "4 to 7 times/week" was associated with increasing BMI (beta = 0.21 kg/m2; 95 percent confidence interval: 0.03-0.39) compared with those with low consumption of FFA at baseline and 1 year later. At baseline, frequency of eating FFA was associated with greater intakes of total energy, sugar-sweetened beverages, and trans fat, as well as lower consumption of low-fat dairy foods and fruits and vegetables. These data suggest that older children who consume greater quantities of FFA are heavier, have greater total energy intakes, and have poorer diet quality. Furthermore, increasing consumption of FFA over time may lead to excess weight gain.

Obesity as Compared With Physical Activity in Predicting Risk of Coronary Heart Disease in Women. *Circulation*, (in press). Li TY, Rana, JS, Manson, JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. The comparative importance of physical inactivity and obesity as predictors of coronary heart disease (CHD) risk remains unsettled. We followed 88,393 women, 34 to 59 years of age, in the Nurses' Health Study from 1980 to 2000. These participants did not have cardiovascular disease and cancer at baseline. We documented 2,358 incidents of major CHD events (including nonfatal myocardial infarction and fatal CHD) during 20 years of follow-up, including 889 cases of fatal CHD and 1,469 cases of nonfatal myocardial infarction. In a multivariate model adjusting for cardiovascular risk factors, overweight and

obesity were significantly associated with increased risk of CHD, whereas increasing levels of physical activity were associated with a graded reduction in CHD risk (P<0.001). In joint analyses of body mass index (BMI) and physical activity in women who had a healthy weight (BMI, 18.5 to 24.9 kg/m2) and were physically active (exercise > or = 3.5 hours/week) as the reference group, the relative risks of CHD were 3.44 (95 percent confidence interval [CI], 2.81 to 4.21) for women who were obese (BMI > or =30 kg/m2) and sedentary (exercise <1 hour/week); 2.48 (95 percent CI, 1.84 to 3.34) for women who were active but obese; and 1.48 (95 percent CI, 1.24 to 1.77) for women who had a healthy weight but were sedentary. In combined analyses of waist-hip ratio and physical activity, both waist-hip ratio and physical activity were significant predictors of CHD, and the highest risk was among women in the lowest category of physical activity and the highest tertile of waist-hip ratio (relative risk = 3.03; 95 percent CI, 1.96 to 4.18). Even a modest weight gain (4 to 10 kilograms) during adulthood was associated with 27 percent (95 percent CI, 12 percent to 45 percent) increased risk of CHD compared with women with a stable weight after adjusting for physical activity and other cardiovascular risk factors. The conclusion was obesity and physical inactivity independently contribute to the development of CHD in women. These data underscore the importance of both maintaining a healthy weight and regular physical activity in preventing CHD.

Human Metabolic and Genetic Core

Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction. *JAMA* 2005;293:43-53. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. The scarcity of data addressing the health effects of popular diets is an important public health concern, especially since patients and physicians are interested in using popular diets as individualized eating strategies for disease prevention. The objective of this study was to assess adherence rates and the effectiveness of four popular diets (Atkins, Zone, Weight Watchers, and Ornish) for weight loss and cardiac risk factor reduction. This was a single-center randomized trial at an academic medical center in Boston, MA, of overweight or obese (body mass index: mean, 35; range, 27-42) adults aged 22 to 72 years with known hypertension, dyslipidemia, or fasting hyperglycemia. Participants were enrolled starting July 18, 2000, and randomized to the four popular diet groups until January 24, 2002. A total of 160 participants were randomly assigned to either Atkins (carbohydrate restriction, n=40), Zone (macronutrient balance, n=40), Weight Watchers (calorie restriction, n=40), or Ornish (fat restriction, n=40) diet groups. After 2 months of maximum effort, participants selected their own levels of dietary adherence. The main outcome measures included 1-year changes in baseline weight and cardiac risk factors and self-selected dietary adherence rates per self-report. Assuming no change from baseline for participants who discontinued the study, mean (SD) weight loss at 1 year was 2.1 (4.8) kilograms for Atkins (21 [53 percent] of 40 participants completed, P = .009); 3.2 (6.0) kilograms for Zone (26 [65 percent] of 40 completed, P = .002): 3.0 (4.9) kilograms for Weight Watchers (26 [65 percent] of 40 completed, P < .001), and 3.3 (7.3) kilograms for Ornish (20 [50 percent] of 40 completed, P = .007). Greater effects were observed in study completers. Each diet significantly reduced the low-density lipoprotein/high-density lipoprotein (HDL) cholesterol ratio by approximately 10 percent (all P<.05), with no significant effects on blood pressure or glucose at 1 year. Amount of weight loss was associated with self-reported dietary adherence level (r = 0.60; P<.001) but not with diet type (r = 0.07; P = .40). For each diet, decreasing levels of total/HDL cholesterol, C-reactive protein, and insulin were significantly associated with weight loss (mean r = 0.36, 0.37, and 0.39, respectively) with no significant difference between diets (P = .48, P = .57, P = .31, respectively). The study concluded that each popular diet modestly reduced body weight and several cardiac risk factors

at 1 year. Overall dietary adherence rates were low, although increased adherence was associated with greater weight loss and cardiac risk factor reductions for each diet group.

Effect of Screening Out Implausible Energy Intake Reports on Relationships Between Diet and BMI. *Obes Res.* 2005; 13:1205-1217. Huang TT, Roberts SB, Howarth NC, McCrory MA. The objective of this study was to present an updated method for identifying physiologically implausible dietary reports by comparing reported energy intake (rEI) with predicted energy requirements (pER), and we examined the impact of excluding these reports. Adult data from the Continuing Survey of Food Intakes by Individuals 1994 to 1996 were used, and pER was calculated from the dietary reference intake equations. Within-subject variations and errors in rEI [coefficient of variation (CV) approximately 23 percent] over 2 days (d), pER (CV approximately 11 percent), and measured total energy expenditure (mTEE; doubly labeled water, CV approximately 8.2 percent) were propagated, where +/-1 SD = CV2(rEI)/d + CV2(pER) + CV2(mTEE) = +/-22 percent. Thus, a report was identified as implausible if rEI was not within 78 percent to 122 percent of pER. Multiple cut-offs between +/-1 and +/-2 SD were tested. The results showed percent rEI/pER = 81 in the total sample (n = 6499) progressively increased to 95 percent in the +/-1 SD sample (n = 2685). The +/-1 to 1.4 SD samples yielded rEI-weight associations closest to the theoretical relationship (mTEE to weight). Weak or spurious diet-BMI associations were present in the total sample; +/-1 to 1.4 SD samples showed the strongest set of associations and provided the maximum N while maintaining biological plausibility. Our methodology can be applied to different data sets to evaluate the impact of implausible rEIs on health outcomes. Implausible rEIs reduce the overall validity of a sample, and not excluding them may lead to inappropriate conclusions about potential dietary causes of health outcomes such as obesity.

Physical Activity and Sedentary Behavior: A Review of Longitudinal Studies of Weight and Adiposity in Youth. *Int J Obes* 2005 (published on line, ahead of print). Must A, Tybor DJ. The aim of this study was to review the published prospective observational studies of the relationship of physical activity and sedentary behavior with the development of overweight and adiposity, emphasizing methodologic issues. Methods used included: sample size; population studied; length of follow-up; assessment of exposure (physical activity, inactivity, or sedentary behavior); assessment of outcome (relative weight, overweight, percent body fatness, or adiposity); and statistical approach, and the main findings were extracted, summarized, and key methodological issues highlighted. In total, 17 studies of physical activity and 15 studies of inactivity/sedentary behavior were identified; as these were not mutually exclusive, 20 unique studies were reviewed. Results were mixed, with most studies showing an inverse association of physical activity with weight or fatness outcomes and/or a direct association of inactivity/sedentary behavior with weight or fatness outcomes. The effects identified were generally of small magnitude. Imprecise measurement of activity exposures likely weakens the observed relationships. Most studies used a pre-post design and had limited duration of follow-up (< or = 2 years). Studies with longer and more frequent follow-up did not always use the most advantageous statistical approach. On balance, the available evidence from prospective observational studies suggests that increased physical activity and decreased sedentary behavior are protective against relative weight and fatness gains over childhood and adolescence. In addition to improved measurement methods, longer and more frequent follow-up as well as truly longitudinal analysis methods would help establish these important prevention and intervention targets and identify subgroups or development periods where interventions would likely be effective.

Transgenic Core

Divergence of Melanocortin Pathways in the Control of Food Intake and Energy Expenditure. *Cell* 123:493-505. Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, Ferreira M, Tang V, McGovern RA, Kenny CD, et al. Activation of melanocortin-4-receptors (MC4Rs) reduces body fat stores by decreasing food intake and increasing energy expenditure. MC4Rs are expressed in multiple CNS sites, any number of which could mediate these effects. To identify the functionally relevant sites of MC4R expression, we generated a loxP-modified, null Mc4r allele (loxTB Mc4r) that can be reactivated by Cre-recombinase. Mice homozygous for the loxTB Mc4r allele do not express MC4Rs and are markedly obese. Restoration of MC4R expression in the paraventricular hypothalamus (PVH) and a subpopulation of amygdala neurons, using Sim1-Cre transgenic mice, prevented 60 percent of the obesity. Of note, increased food intake, typical of Mc4r null mice, was completely rescued while reduced energy expenditure was unaffected. These findings demonstrate that MC4Rs in the PVH and/or the amygdala control food intake but that MC4Rs elsewhere control energy expenditure. Disassociation of food intake and energy expenditure reveals unexpected divergence in melanocortin pathways controlling energy balance.

Liver-specific Protein-Tyrosine Phosphatase 1B (PTP1B) Re-expression Alters Glucose Homeostasis of PTP1B-/-Mice. *J Biol Chem* 280:15038-15046. Haj FG, Zabolotny JM, Kim YB, Kahn BB, Neel BG. Protein-tyrosine phosphatase 1B (PTP1B) is an important negative regulator of insulin and leptin signaling *in vivo*. Mice lacking PTP1B (PTP1B-/- mice) are hyper-responsive to insulin and leptin and resistant to diet-induced obesity. The tissue(s) that mediate these effects of global PTP1B deficiency remain controversial. We exploited the high degree of hepatotropism of adenoviruses to assess the role of PTP1B in the liver. Liver-specific reexpression of PTP1B in PTP1B-/- mice led to marked attenuation of their enhanced insulin sensitivity. This correlated with, and was probably caused by, decreased insulin-stimulated tyrosyl phosphorylation of the insulin receptor (IR) and IR substrate 2-associated phosphatidylinositide 3-kinase activity. Analysis using phospho-specific antibodies for the IR revealed preferential dephosphorylation of Tyr-1162/1163 compared with Tyr-972 by PTP1B *in vivo*. Our findings show that the liver is a major site of the peripheral action of PTP1B in regulating glucose homeostasis.

Adipocyte-specific Glucocorticoid Inactivation Protects Against Diet-induced Obesity. *Diabetes* 54:1023-1031. Kershaw EE, Morton NM, Dhillon H, Ramage L, Seckl JR, Flier JS. Local glucocorticoid (GC) action depends on intracellular GC metabolism by 11beta-hydroxysteroid dehydrogenases (11betaHSDs). 11betaHSD1 activates GCs, while 11betaHSD2 inactivates GCs. Adipocyte-specific amplification of GCs through transgenic overexpression of 11betaHSD1 produces visceral obesity and the metabolic syndrome in mice. To determine whether adipocyte-specific inactivation of GCs protects against this phenotype, we created a transgenic model in which human 11betaHSD2 is expressed under the control of the murine adipocyte fatty acid binding protein (aP2) promoter (aP2-h11betaHSD2). Transgenic mice have increased 11betaHSD2 expression and activity exclusively in adipose tissue, with the highest levels in subcutaneous adipose tissue, while systemic indexes of GC exposure are unchanged. Transgenic mice resist weight gain on high-fat diet due to reduced fat mass accumulation. This improved energy balance is associated with decreased food intake, increased energy expenditure, and improved glucose tolerance and insulin sensitivity. Adipose tissue gene expression in transgenic mice is characterized by decreased expression of leptin and resistin and increased expression of adiponectin, peroxisome proliferator-activated receptor gamma, and uncoupling

protein 2. These data suggest that reduction of active GCs exclusively in adipose tissue is an important determinant of a favorable metabolic phenotype with respect to energy homeostasis and the metabolic syndrome.

Specific Accomplishments

BONRC and Core laboratory activities that have helped to further the understanding of obesity and its associated causes and consequences include the following:

Administrative Core. The Administrative Core, through coordination of the Enrichment Program, has offered new and current investigators in obesity research the opportunity to hear experts in the field present information on a variety of topics. In the past year, BONRC has shared the responsibility of coordinating and hosting a monthly seminar series with Dr. Allan Walker's Clinical Nutrition Research Center at Harvard University. The seminars co-sponsored by the two Nutrition Research Centers continue to attract a broad and diverse audience, and the interchange that occurs at these seminars stimulates new directions and interactions among our investigators. The ongoing participation by the Center investigators in the joint Harvard Tufts continuing medical education course (G.L. Blackburn, Course Director) provides a highly visible and popular mechanism to transfer the most recent findings on obesity into clinical practice. In addition, the Center hosted its annual half-day retreat at Boston University School of Medicine on June 27, 2005. Featured speakers in the plenary session included Lee M. Kaplan, M.D., Ph.D. (Massachusetts General Hospital); Steven B. Heymsfield, M.D. (Merck Research Laboratories); and Philipp E. Scherer, Ph.D. (Albert Einstein College of Medicine). A total of twenty-one posters were displayed in the poster session.

Adipocyte Core. The purpose of the Adipocyte Core continues to be to provide euploid rodent and human undifferentiated and differentiated mass-cultured and cloned preadipocytes and freshly-isolated and cultured fat cells and products derived from these cells (RNA, DNA, protein, conditioned medium) cost-efficiently to BONRC investigators. Extensive quality control and continuous quality assurance procedures are followed in preparing these products. The Core makes available methods for measuring the replication and differentiation of preadipocytes; teaches methods for preparing preadipocytes, fat cells, and their products; and provides consultative advice about experimental designs involving these preparations. The Core maintains a bank of human preadipocytes and now regularly obtains human adipose tissue from both Boston University and New England Medical Center. The Core fosters collaborative links among investigators in adipose biology and provides assistance to investigators new to the field. A well attended bimonthly adipose biology seminar series is run by the Core. Consultation on projects proposed by various investigators has continued to be a primary function of the Core.

Epidemiology/Biostatistics Core. The Epidemiology/Biostatistics Core provides a mechanism for researchers who want to apply clinical and cellular knowledge to applications in ongoing epidemiological studies. In addition, the Core provides a center for consultation and training on methodological and statistical issues. Specific activities include the following: providing consultation on study design, sample size, statistical analyses, and power for members of the Obesity Center; making available data sets to address questions central to the study of obesity; and providing consultations on study design, questionnaire design, and statistical analyses to researchers working in the fields of obesity and nutrition.

Human Metabolic and Genetic Core. The Human Metabolic and Genetic Core at Tufts/New England Medical Center and Tufts University serves to characterize the phenotypic expression of overnutrition and undernutrition as well as altered nutritional states induced by disease states and aging. Secondly, the Core is designed to quantify the impact of a variety of nutritional intervention strategies on the disorders under study in the Core. The Core serves members of the BONRC whose research requires measurements of body composition, fat distribution, metabolic rate or energy expenditure, and substrate utilization.

Transgenic Core. The Transgenic Core continues to make important advances in the application of transgenic mouse models to the area of obesity research. Users of the BONRC Transgenic Core are among the most important group of contributors to this field in the world today. In addition to the development of transgenic mice, the Core offers knockout mice and continues to offer consultation to many investigators on construct preparation and training in microinjection and embryo transfer.

Educational Activities/Accomplishments

Enrichment Program. This program represents an approach that amplifies the central themes of the BONRC and draws together the various groups and institutions that comprise the BONRC. The main goals of this program are to:

- Support a monthly seminar series;
- Participate in the ongoing continuing medical education course co-sponsored by Harvard Medical School, Tufts University School of Medicine, and the North American Association for the Study of Obesity (NAASO);
- Provide support for minisymposia or visiting scientists;
- Provide financial support for junior investigators to attend conferences related to obesity and nutrition research; and
- Host an annual program.

Boston Nutrition Seminars. The BONRC and the Harvard CNRU cosponsor the Boston Nutrition Seminars. The monthly seminars present speakers on a variety of obesity and nutrition topics and invite participants to become involved in the ONRC's and CNRU's activities. Both Boston-area and visiting scientists have served as speakers for the seminars, which have been well attended and enthusiastically received. The topics presented in the 2004-2005 and 2005-2006 (in process) series included:

- Role of Calcium Nutrition and Other Lifestyle Factors in Bone Health. Connie M. Weaver, Ph.D., Head and Distinguished Professor of Department of Foods and Nutrition, Purdue University and Director of NIH Botanicals Center for Age-related Diseases.
- Can (or Should) Obesity be Treated Pharmacologically? Nicholas Finer, MBBS, FRCP, R. Nutr., Clinical Director, Wellcome Trust Clinical Research Facility and Senior Research Associate, Cambridge University.
- Improving Infant Formulas: Role in Lifelong Nutritional Health. Sharon M. Donovan, Ph.D., RD, Professor of Nutrition, Melissa M. Noel Endowed Chair in Diet and Health, Department of Food Science & Human Nutrition, University of Illinois at Urbana.
- Regulation of VLDL Secretion from the Liver: Fatty Acids, Fats, and Nuclear Receptors. Henry Ginsberg, M.D., Herbert Irving Professor of Medicine, Division of Preventive Medicine, Presbyterian Hospital.

- Role of Dietary Modification in Cancer Prevention. Jin-Rong Zhou, Ph.D., Assistant Professor of Surgery, Department of Surgery, Harvard Medical School and Director, Nutrition/Metabolism Laboratory, Beth Israel Deaconess Medical Center.
- Role of the Adipocyte, Free Fatty Acids, and Ectopic Fat in the Pathogenesis of Type 2 Diabetes Mellitus. Ralph A. DeFronzo, M.D., Professor of Medicine and Chief of the Diabetes Division, University of Texas Health Science Center and the Audie L. Murphy Memorial VA Hospital, San Antonio, Texas and Deputy Director of the Texas Diabetes Institute.
- Molecular Physiology of Weight Regulation. Rudolph Leibel, M.D., Co-Director, Naomi Berrie Diabetes Center, Professor of Pediatrics and Medicine, Head, Division of Molecular Genetics, Columbia University.
- A Genetic Signature Present in 10 percent of Individuals is Associated with Adult and Childhood Obesity. Michael Christman, Ph.D., Professor and Chair, Department of Genetics and Genomics, Boston University School of Medicine.
- Utilizing Zebrafish to Elucidate the Role of Nutrition in Early Development. Jonathan Gitlin, M.D., Helen B. Roberson Professor of Pediatrics, Washington University School of Medicine.

Symposium. The BONRC holds an annual half day symposium in conjunction with a meeting with the Scientific Advisory Committee. The program includes both a plenary and poster session.

Adipose and Metabolic Tissue Study Group. This series is co-sponsored by the Adipocyte Core and consists of research seminars, presentations of research in progress, and grant proposals for critical review. Meeting topics in the 2004-2005 and 2005-2006 (in process) series included:
- NF-kB Mediated Inflammation in Fat and Liver: Pathogenic Mediator in Insulin Resistance and Pharmacologic Target for Reversal. Steven Shoelson, M.D., Ph.D., Joslin Diabetes Center.
- Functional Heterogeneity of Mitochondria within the Single Beta Cell. Orian S. Shirihai, M.D., Ph.D., Tufts University.
- Perilipin Update: Estrogen Regulation of Metabolism. Andrew Greenberg, M.D. and Tara D'Eon, M.S., Tufts University.
- Molecular Mechanisms for GLUT4 Glucose Transporter Trafficking. Jonathan Bogan, M.D., Yale University School of Medicine.
- Regional Variation in Preadipocyte Function: Are Different Fat Depots Separate Mini-Organs? James L. Kirkland, M.D., M.Sc., Ph.D., Boston University School of Medicine.
- Catecholamine-Regulated Kinase Pathways in Lipolysis and Thermogenesis. Sheila Collins, Ph.D., CIIT Centers for Health Research.
- Roles and Regulation of PTP1B in Insulin-Resistance and Obesity. Janice Zabolotny, Ph.D., Beth Israel Deaconess Medical Center.
- Transcriptional Control of Lipid and Energy Homeostasis. Bruce Spiegelman, Ph.D., Dana-Faber Cancer Institute.
- UCP2 and Pancreatic Beta-Cell Dysfunction. Bradford B. Lowell, M.D., Ph.D., Beth Israel Deaconess Medical Center.
- Fatty Acid Flip-flop in Membranes: Why is it Still Controversial, and Could it Explain the Origin of Life? James Hamilton, Ph.D., Boston University School of Medicine.
- Role of the Ventromedial Hypothalamus in Body Weight Regulation by Leptin. Harveen Dhillon, Ph.D., Beth Israel Deaconess Medical Center.

- Mechanistic Basis and Role of Perilipin in Regulating Lipolysis and Adaptive Thermogenesis. Andrew Greenberg, M.D., Tufts University.
- A Mechanism for the Thrifty Phenotype. Barbara E. Corkey, Ph.D., Boston University School of Medicine.
- Tissue-specific Deletion of PTP1B: Insights into Body Mass Control and Glucose Homeostasis. Kendra Bence, Ph.D., Beth Israel Deaconess Medical Center.
- Central and Peripheral Regulation of Nutrient Homeostasis by the Insulin Signaling Cascade. Morris White, Ph.D., Joslin Diabetes Center.

Enrichment Funds. Enrichment funds for junior investigators are offered for specific obesity/nutrition related conferences. Announcements about the availability of scholarship funds are mailed to all BONRC members. In addition, core directors are encouraged to promote the availability of these funds to interested, eligible staff.

Benefits and Interactions Resulting From the Existence of the ONRC

The enrichment program continues to provide an important mechanism to increase the visibility of the BONRC in the Boston area. The Executive Committee as well as individual core laboratories continue to organize additional programs to enhance collaborative research efforts. The joint sponsorship of the Boston Nutrition Seminars with the CNRU at Harvard has broadened the scope of the evening lectures to include both nutrition and obesity. We anticipate that the BONRC's continued sponsorship of such discussions will help identify gaps in research that might be addressed by new research proposals. Regardless, such discussions should help promote discussions between basic and clinical scientists, an area that the BONRC continues to assess and develop.