Pennington Scientific Symposium

Adaptive Thermogenesis and Human Obesity

December 8 - 9, 2008

Symposium Chairs

Claude Bouchard, PhD
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This symposium was coordinated by the
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Monday, Dec. 8
All symposium meetings will be held in the Abell Board Room of the Lod Cook Alumni Center (LSU Main Campus).

SESSION CHAIR: Jean-Pierre Flatt, PhD
8:30-9:30  Claude Bouchard, PhD
Pennington Biomedical Research Center
Introduction, Objectives and Definitions

9:30-10:30  Leslie Kozak, PhD
Pennington Biomedical Research Center
Evidence for the presence of adaptive thermogenesis in rodents

10:30-10:45  BREAK

10:45-11:45  Dale Schoeller, PhD
University of Wisdomon, Madison
Evidence from overfeeding studies in humans

11:45-12:45  LUNCH

SESSION CHAIR: Eric Ravussin, PhD
1:00-2:00  Eric Ravussin, PhD
Pennington Biomedical Research Center
Evidence from underfeeding studies in humans

2:00-3:00  Kevin Hall, PhD
NIH, NIDDK
Modeling adaptive thermogenesis in overfeeding and underfeeding

3:00-3:15  BREAK

3:15-4:15  Angelo Tremblay, PhD
Université Laval
Evidence from exercise and clinical studies in humans

4:15-4:45  Patrick Seale, PhD – Scientific Colleague of Dr. Kozak
Postdoctoral Fellow, Dana-Farber Cancer Institute
Brown fat cell determination
Ed Melanson, PhD – Scientific Colleague of Dr. Tremblay
Associate Professor, Univ. of Colorado School of Medicine
Weight loss induced changes in exercise energy expenditure: Important experimental considerations
Yann Ravussin – Scientific Colleague of Dr. Rosenbaum
Graduate Student, Columbia University
Molecular physiological adaptations to weight perturbations in C57BL/6J mice

5:00 – 7:00  Hospitality Suite Open (#528)

7:00  Dinner - Lod Cook Alumni Center

9:00  Hospitality Suite Open (#528)
Monday, Dec. 9

All symposium meetings will be held in the Abell Board Room of the Lod Cook Alumni Center (LSU Main Campus).

SESSION CHAIR: Angelo Tremblay, PhD
8:30-9:30
Jan Nedergaard, PhD
Stockholm University
UCP’s and BAT as potential mechanisms for adaptive thermogenesis in humans

9:30-10:30
Denis Richard, PhD
Université Laval
Human brown adipose tissue and SNS mediated thermogenesis in humans

10:30-10:45 BREAK

10:45-11:45
Michael Rosenbaum, MD
Columbia University College of Physicians & Surgeons
Skeletal muscle metabolism as a potential mechanism for adaptive thermogenesis in humans

11:45-12:45 LUNCH

SESSION CHAIR: Claude Bouchard, PhD
1:00-2:00
Rudy Leibel, MD
Columbia University
Adaptive thermogenesis influences body weight regulation

2:00-3:00
Jean-Pierre Flatt, PhD
University of Massachusetts Medical School
Adaptive thermogenesis does not influence body weight regulation

3:00-3:15 BREAK

3:15-5:00
Consensus Discussion
Development of a document on the role of adaptive thermogenesis in the regulation of body weight in humans and on key research questions

5:00 – 7:00 Hospitality Suite Open (#528)

7:00 Dinner - Lod Cook Alumni Center

9:00 Hospitality Suite Open (#528)
The aim of this symposium is to critically review the evidence for a role of adaptive thermogenesis and its potential impact in human obesity. For the purpose of the symposium, it is proposed to define adaptive thermogenesis as resulting from changes in resting expenditure not attributable to changes in resting metabolic rate, thermic effect of food and other energy expenditure components or to changes in the size of tissues and organs in response to disturbed energy balance. The main goals of the symposium area: to achieve a consensus on a definition of adaptive thermogenesis; to examine the scope of adaptive thermogenesis in humans; do define its impact on the rate of body weight variation in response to overfeeding, caloric restriction and other conditions; to describe the mechanisms involved in adaptive thermogenesis; and to assess the significance of adaptive thermogenesis in the development of obesity in human populations. A potential adaptive thermogenesis response to cold, exercise or drug exposure will also be examined. Evidence for controlled overfeeding studies in humans will be reviewed with the goal of identifying the presence or not of an adaptive thermogenic component, particularly in the long term studies. The same review will be performed for negative energy balance experiments in which the caloric deficit was generated by caloric restriction, standardized exercise prescription or a combination of both. The issue of whether or not there is adaptive thermogenesis in people in response to prolonged alterations in energy balance conditions designed to induce weight gain or weight loss is one that has generated heated discussion over a few decades. It continues to be re-visited from time to time as new evidence becomes available. The recent observation that overfeeding and cold induced adaptive thermogeneses were correlated is of particular interest. It suggests that they share common mechanisms and that there may be individuals who have a greater ability to compensate excess caloric intake, caloric restriction and other alterations in energy balance conditions compared to others.
Evidence for the presence of adaptive thermogenesis in rodents

Leslie P. Kozak, PhD. and Rea Anunciado-Koza, PhD
Molecular Genetics and Thermogenesis
Pennington Biomedical Research Center, LSU System, Baton Rouge, LA

For the past 30 years a key hypothesis in obesity research has stated that when an individual enters a positive state of energy balance a thermogenic process is activated by the central nervous system (CNS) that increases substrate oxidation to bring the individual back into energy balance. A corollary is that defects in either the activation mechanism, presumably in the hypothalamus and closely tied to centers of food intake, or in the thermogenic process itself, located peripherally, will lead to disruptions on body composition, that is obesity (1).

The major obstacle to testing this hypothesis in humans has been our inability to identify peripheral thermogenic mechanisms, although recent evidence on the presence of brown adipocytes in humans may change this. Hence, tests of the hypothesis have come from a range of studies in mice and rats, since the requirements of these smaller-sized species for survival in a cold environment led to the evolutionary development of brown fat (BAT), an extremely effective and efficient thermogenic tissue whose mechanism of heat generation is based upon uncoupling of oxidative phosphorylation by the mitochondrial uncoupling protein (UCP1). From 1979 when Rothwell and Stock (2) published a paper in Nature on diet-induced thermogenesis in rats until 1997 with the advent of a target gene mutation that inactivated $Ucp1$ (3), pharmacological, dietary energy balance studies as well as studies with leptin/leptin receptor null mice generated evidence that was interpreted as supporting a role for UCP1 in the regulation of body weight/obesity (4). It was therefore expected that inactivation of $Ucp1$ would reduce the thermogenic capacity to burn fat and increase obesity, particularly when mice were forced into a state of positive energy balance by feeding a high fat diet. It was surprising therefore when $Ucp1$-deficient mice were not obese, rather they showed resistance to diet-induced obesity.

Importantly, the $Ucp1$-deficient mice could not tolerate acute exposure to a cold environment ($4^\circ$C), since shivering was not able to generate sufficient heat to maintain normal body temperature. However, if the ambient temperature was gradually reduced the mice could survive at $4^\circ$C for several days (5). This indicated that an alternative thermogenic mechanism could be induced to maintain normal body temperature. There was a metabolic cost to the mice for this adaptive protective thermogenic response. Mice raised at a lower temperature ($20^\circ$C) consumed more calories and were leaner (6). Accordingly, we concluded that the while alternative thermogenesis could maintain body temperature in $Ucp1^{-/-}$ mice, it was not as efficient as BAT nonshivering thermogenesis. If alternative thermogenesis is metabolically less efficient, then it may provide a mechanism in species like humans that have a paucity of brown adipocytes. We have developed a strategy to find and assess the physiological effects of alternative thermogenic mechanism by combining the $Ucp1^{-/-}$ mutation with other mutations with putative thermogenic functions. Two genes that have been tested are $ob$ and $Gdm$, the latter encodes the mitochondrial glycerol phosphate dehydrogenase. No phenotypic differences between $ob/ob$ and $Ucp1^{-/-}ob/ob$. mice were detected suggesting that UCP1-based thermogenesis is not essential for the regulation of adiposity in $ob/ob$ mice at temperatures between 21 and 28$^\circ$C(7). The $Ucp1^{-/-}$. $Gdm^{-/-}$ mouse has been particularly informative, since this double mutant mouse cannot tolerate the cold, although $Gdm^{-/-}$ are not cold sensitive (8). When $Ucp1^{-/-}$. $Gdm^{-/-}$ mice are fed at high fat diet at 20$^\circ$C they resist obesity similar to $Ucp1^{-/-}$; however, in contrast to $Ucp1^{-/-}$ mice they continue to resist diet-induced obesity even after the ambient temperature has been increased to 28$^\circ$C. Histological and gene expression analysis indicate that the site for this inducible thermogenesis is the inguinal fat depot and it is accompanied by mass induction of an adipocyte resembling the brown adipocyte, but without UCP1 or GDM and with no evidence for involvement of liver or skeletal muscle. The inguinal fat has increased oxygen consumption and we propose it has enhanced thermogenic capacity based upon an increase in other mitochondrial solute carriers and $Ca^{++}$ cycling (8).
Our experience with the \textit{Ucp1}\textsuperscript{-/-} mice suggests that UCP1 can be involved in body weight regulation, but only indirectly when the animal is forced to respond to the need to generate heat to maintain body temperature. In addition, diet-induced thermogenesis of \textit{Ucp1}\textsuperscript{-/-} mice, that is, increased oxygen consumption when fed high fat-high sucrose diets, is indistinguishable from that of wild type mice (8). A question remains on how to interpret the large numbers of transgenic mouse models in which up-regulation of \textit{Ucp1} or increased numbers of brown adipocytes results in reduced adiposity. In virtually all of these models the transgenic \textit{Ucp1} gene 1.) is not regulated by normal mechanisms involving the sympathetic nervous system, 2.) is over-expressed due to the effects of reduced environmental temperature or 3.) is induced with a pharmacological agent, e.g. β3-adrenergic agonists. Thus, it is possible to utilize the brown adipocyte system for body weight regulation by circumventing its normal function and/or regulation by genetic or pharmacological methods. However, with respect to thermogenic mechanisms that regulate body weight in a state of positive energy balance these experiments suggest that under normal physiological conditions there is no adaptive thermogenesis for the regulation of body weight in mice, only for the regulation of body temperature.

\textbf{References:}

Overfeeding studies in humans: A review of the literature

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It is clear that energy expenditure in humans generally increases with increases in energy intake above maintenance requirements, but the magnitude and degree of individual variation are still controversial. These two questions are probably as old as civilization, but as scientific questions they date to the early 1900s, when investigators studied the effects of large increases in energy intake on body weight and reported what they concluded to be only modest increases in weight. Between 1960 and 1990, these overfeeding studies have been repeated with greater control and using larger samples. A general finding from these studies was that average weight gains were less than expected from energy balance calculations and that individual variations in weight gain were large suggesting that energy expenditure increases during overfeeding and that it can offset the increase in energy intake in a large fraction of the young adults. This potential to increase energy expenditure has been termed adaptive thermogenesis or luxuskonsumption. Most actual measures of energy expenditure, however, have been limited to measures of resting metabolic rate and perhaps the thermic effect of meals because the measurement of human energy expenditure has been hampered by the limitations of instruments to make such measurements. Multiple over- and underfeeding studies have been performed. Despite the measurement limitations, these studies, however, have demonstrated that resting metabolic rate does vary when energy intake differs from a weight maintenance energy requirement. Theses changes in energy expenditure, however, are not large enough to account for the individual variations in weight change, but this is not surprising considering the limited portion of the day during which energy expenditure is measured. Only since the doubly labeled water method has been applied to the measurement of human energy expenditure has it been possible to design studies in which all routes of energy expenditure can be measured during energy imbalance and thus fully address this question.

To date there have been 9 studies of energy balance involving 81 participants that have employed doubly labeled water to measure energy expenditure during overfeeding (Table 1).

Among these studies, only one found an average increase in total energy expenditure that accounted for over half of the excess dietary intake. This study of non-obese individuals by Levine et al (1999) was of note because the increase in total energy expenditure was strongly inversely correlated with weight gain \(r=-0.77\). In contrast, the weighted average for the increase in total energy expenditure from the other eight studies was 11%. Of these eight studies, four published individual data (Bandini, Diaz, Riumallo and Siervo), and it was possible to repeat the correlation analysis of Levine et al. The relationship in these studies was significant, but less strong, accounting for only 25% of the variance in weight gain \(r=-0.47\). There was no correlation with either body mass index at baseline or the length of the study.

The increases in total energy expenditure were not typical of classical overfeeding thermogenesis as reported in laboratory animals. The correlation with change in resting metabolic rate under basal or near basal conditions (RMR) was positive and weak \(r=0.22\). The thermic effect of meals was only reported in three studies. Of these, Leven et al (1999) reported an increase equal to 13% of the excess energy intake, and Bandini et al (1989) and Pasquet et al (1992) reported 6 and 13%, respectively. By deduction it is concluded that the increase in total energy expenditure reported by Levine as well as that observed to a smaller degree in the other eight studies must largely be explained by changes in non-resting energy expenditure. In the study by Levine et al (), this increase, although equal to 75% of the excess in one individual, was not detected by a physical activity monitor and thus was concluded that the increase was in non-exercise activity thermogenesis. In the remaining studies, the average increase in nonresting energy expenditure accounts for less than 15% of the excess energy intake. Of note, these changes in activity energy during overfeeding include both decreases and increases. This is observed both in the averages of individual studies and in the individual
values in those four studies that published individual data. Thus, the impact of overfeeding on activity energy expenditure is not consistent, although it should be remembered that this term of energy expenditure cannot generally be measured with great precision. Moreover, it is not clear if the changes in activity energy expenditure are volitional or nonvolitional. Indeed, the person in the study by Diaz et al (1992) who displayed the largest increase in activity energy expenditure reported during a post-study debriefing that he had begun an exercise program during the overfeeding portion of the study that involved 40-60 min/d of running or cycling.

In conclusion, the published studies of over-feeding in humans in which total energy expenditure was measured do not support the hypothesis the adaptive thermogenesis can obviate the effects of overeating on weight gain. On an individual basis, there is evidence that a few individuals can obviate weight gain though increases in activity energy expenditure, but it is not clear what fraction of this is volitional activity rather than an adaptive mechanism. There does remain a large individual variation in weight gain during overfeeding that remains unexplained. Possible explanations include failure to consume all of the diets during outpatient studies, variation in the composition of the weight gain, and measurement error in the determination of maintenance energy requirements and other study outcomes.

### Table 1. Studies of energy overfeeding with measures of total energy expenditure (mean±SD)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Excess Ein kcal/d * days</th>
<th>Change in RMR % of excess Ein</th>
<th>Change in TEE % of excess Ein</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bandini (1989)</td>
<td>6m/3f</td>
<td>1500±14</td>
<td>13±7</td>
<td>10±19</td>
<td>Adolescents</td>
</tr>
<tr>
<td>Riumali (1989)</td>
<td>5m/0f</td>
<td>750±84</td>
<td>2</td>
<td>-6±14</td>
<td>Lean adults</td>
</tr>
<tr>
<td>Roberts (1990)</td>
<td>7m/0f</td>
<td>1000±21</td>
<td>5</td>
<td>19</td>
<td>Adults</td>
</tr>
<tr>
<td>Pasquet (1992)</td>
<td>9m/0f</td>
<td>2950±64</td>
<td>18</td>
<td>0±22</td>
<td>Lean adults</td>
</tr>
<tr>
<td>(Guru Walla)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diaz (1992)</td>
<td>7m/0f</td>
<td>1500±42</td>
<td>14±6</td>
<td>29±29</td>
<td>Adults</td>
</tr>
<tr>
<td>Saltzman (1996)</td>
<td>9m/0f</td>
<td>1000±21</td>
<td>8</td>
<td>55</td>
<td>Elderly</td>
</tr>
<tr>
<td>Levine (1999)</td>
<td>12m/4f</td>
<td>1000±56</td>
<td>8</td>
<td>55</td>
<td>Adults</td>
</tr>
<tr>
<td>Joosen (2005)</td>
<td>0m/14f</td>
<td>1340±14</td>
<td>7</td>
<td>7</td>
<td>Adults</td>
</tr>
<tr>
<td>Sievor (2008)</td>
<td>5m/0f</td>
<td>1630±21</td>
<td>14±7</td>
<td>28±16</td>
<td>Adults</td>
</tr>
</tbody>
</table>

### References:


Evidence from underfeeding studies in humans

Eric Ravussin, PhD
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For weight maintenance, not only does energy intake have to match energy expenditure but macronutrient intake must balance macronutrient oxidation. However, this equilibrium seems to be particularly difficult to achieve in individuals with low fat oxidation, low energy expenditure, low sympathetic activity or low levels of spontaneous physical activity, since in addition to excess energy intake, all of these factors explain the tendency of some people to gain weight. Additionally, large variability in weight change is observed when energy surplus is imposed experimentally or spontaneously. Clearly, the data suggest a strong genetic influence on body weight regulation implying a normal physiology in an “obesogenic” environment. The societal environment is marked by overabundant accessibility to food coupled with reduced physical activity leading to the metabolic syndrome in most individuals.

Energy homeostasis is however critical for the survival of species. Therefore, multiple and complex mechanisms have evolved to regulate energy intake and expenditure in order to maintain body weight in periods of energy deficit. Not surprisingly, in response to energy restriction, most people fail to maintain the new lower body weight because of a combination of “metabolic adaptations” and environmental “obesogenic” factors both conducive to weight relapse. The focus of my presentation will be on a review of the literature regarding the energy metabolism responses to calorie restriction (CR) in obese, overweight and normal-weight individuals.

We will emphasize some of our own studies of metabolic and behavioral adaptations to caloric restriction in free-living conditions. In a recent study at our Center, 48 (36.8±1.0y), overweight (BMI 27.8±0.7kg/m²) participants were randomized to four groups for 6-months; Control: energy intake at 100% of energy requirements; CR: 25% calorie restriction; CR+EX: 12.5% CR plus 12.5% increase in energy expenditure by structured exercise; LCD: low calorie diet (890kcal/d) until 15% weight reduction followed by weight maintenance. Body composition (DXA), total daily energy expenditure (TDEE) over 14-days by doubly labeled water (DLW), 24-h sedentary energy expenditure by a respiratory chamber and activity related energy activity (AREE) were measured after 3 (M3) and 6 (M6) months of intervention. Weight changes at M6 were –1.0±1.1% (Control), –10.4±0.9% (CR), –10.0±0.8% (CR+EX) and -13.9±0.8% (LCD). At M3, absolute TDEE was significantly reduced in CR (-454±76 kcal/d) and LCD (-633±66 kcal/d) but not in CR+EX or controls. At M6 the reduction in TDEE remained lower than baseline in CR (-316±118 kcal/d) and LCD (-389±124 kcal/d) but reached significance only when CR and LCD were combined. In this combined groups (CR/LCD), TDEE adjusted for body composition, was significantly lower by -431±51 and -240±35 kcal/d at M3 and M6, respectively, indicating a clear metabolic adaptation. Similarly, after adjustment for changes in body composition, sedentary 24h energy expenditure (respiratory chamber) was decreased in CR (-135±42 kcal/d), CREX (-117±52 kcal/d) and LCD (-125±35 kcal/d) i.e. approximately 6-7% more than expected on the basis of the loss in fat-free mass and fat mass. Importantly, physical activity (TDEE adjusted for sleeping metabolic rate) was significantly reduced from baseline at month 3 but tended to return towards baseline at month 6. We therefore showed for the first time in free-living conditions that CR results in a metabolic adaptation and a behavioral adaptation with decreased physical activity levels. These data also indicate how CR may causes large inter-individual variability in the rates of weight loss even in fully adherent individuals and how exercise may influence weight loss and weight loss maintenance. Some data from the weight loss registry will be briefly presented.

Interestingly, CR increased muscle expression of genes involved in mitochondrial biogenesis including PGC1-α, mtTFA, endothelial nitric oxide, SIRT1 and PARL. In parallel, mitochondrial content increased by 35±5% in this group. This study therefore supports the “rate of living”
theory of aging mediated by a potential improvement in mitochondrial function associated with decreased DNA damage.

From the above study, we also estimated the percent of CR maintained from baseline to month 3 and baseline to month 6 from the intake:balance equation assuming that during CR, energy intake equals energy expenditure plus changes in energy stores. Energy expenditure was measured by doubly labeled water and changes in energy stores (fat mass and fat-free mass) were determined by DXA. Pearson correlation analyses of calorie restriction vs. several outcome variables revealed that after 3 and 6 months of intervention the degree of CR was negatively associated with 24h energy expenditure ($p<0.001$), fasting T3 ($p<0.01$), total cholesterol ($p<0.01$), LDL-C ($p<0.01$), leptin ($p<0.01$) and ghrelin ($p<0.01$). An important question is to determine whether these variables are being modulated as a function of weight or body composition changes independent of calorie restriction. Only longer studies with maintenance of weight loss will allow us to disentangle the effect of weight loss vs. caloric restriction.

We will present some of the design features of our ongoing 2-year study in which we are (Pennington, Washington University and Tufts University) recruiting and randomizing (2/1) 250 volunteers to a 25% CR group vs. controls.
Modeling Adaptive Thermogenesis in Over-feeding and Under-feeding

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Laboratory of Biological Modeling, NIDDK, NIH, Bethesda, MD

The biophysical bases of the whole-body energy expenditure rate are the energy-consuming cellular processes that maintain the non-equilibrium thermodynamic state of the body, along with the work rate to perform physical activity. The cellular processes include the Na/K and Ca ATPases that maintain ion concentration differences across cellular membranes, macromolecular synthesis and degradation, metabolic substrate cycles, and the maintenance of the mitochondrial proton gradient [1, 2]. Adult human resting energy expenditure can vary by more than 1000 kcal/d [3], presumably due to variations of the number of cells in the body as well as differences in the magnitudes of the above cellular fluxes.

Since these cellular processes cannot presently be measured at a whole-body level, mathematical modeling of human energy expenditure requires the use of other variables as inputs that are related to these more fundamental cellular processes. For example, it is well known that body fat mass contributes less to resting energy expenditure than fat-free mass and linear regression models have been used to quantify these relationships [3]. At the next level of detail, a more realistic model would include individual organ masses [4-6] since specific metabolic rates of various organs can vary by as much as two orders of magnitude, with adipose tissue having the lowest specific metabolic rate [7]. These differences between organ metabolic rates presumably derive from varying cellular fluxes across different organs. Finally, any information about changes of the energy-consuming cellular processes can be used to augment mathematical models of energy expenditure based on body composition alone [8].

Because adaptive thermogenesis is defined as the change of energy expenditure that is unaccounted for by known model variables, mathematical models are required to determine its existence and magnitude. Here, I will present various mathematical models of human energy expenditure at different levels of complexity based on available data. We consider models and data from both steady-state weight change [9] as well as the dynamic phases of weight gain and loss [8]. These models will be used to determine whether there is a missing contribution to the measured changes of energy expenditure that are unaccounted for by the model variables. To quantify the magnitude of adaptive thermogenesis, we introduce a new model parameter that is driven by the energy intake rate and whose value was determined to minimize the difference between the model predictions and the experimental data.

References:


Thermogenesis in humans: Evidence from exercise and clinical studies

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The environmental factor that has the greatest potential to modify daily energy needs is physical activity whose the energy cost can impose major changes in non resting daily energy expenditure. Beyond this effect, numerous studies have shown that the impact of exercise on energy expenditure may exceed its energy cost, possibly because of an increase in post-exercise resting metabolic rate (RMR). We undertook the investigation of this issue about 25 years ago when we tested exercise-trained individuals who were compared to sedentary subjects. In each group, we observed a positive relationship between RMR and fat-free mass but the level of the regression line was greater in the trained group. This difference corresponded to 100-200 kcal/day and was subsequently found to represent a short term stimulation persisting for one to several days after exercise. In addition, the study of the effects of physical activity modalities on RMR suggested that the increase in exercise intensity favors an accentuation of the post-exercise increase in RMR and fat oxidation. From a mechanistic standpoint, this effect is perceived as concordant with the demonstration that the beta blockade propranolol markedly reduced the post-exercise stimulation of RMR, be it in endurance-trained athletes or in sedentary subjects tested after a vigorous exercise. The use of exercise training protocols to modify RMR revealed the existence of a genotype-exercise interaction effect being reflected by the significantly greater within-pair resemblance in RMR change in monozygotic twins subjected to this protocol. Taken together, these observations demonstrate that exercise is a stimulus that can stimulate RMR to a significant extent beyond what could be predicted by body weight or its components. Conversely, some of our studies showed that the thermic response to a meal or glucose was reduced in trained subjects displaying an increased RMR.

Beyond the characterization of the thermogenic effect of exercise, we and other scientists have committed a lot of effort to identify and quantify a thermogenic defect in obesity-prone people. The underlying preoccupation in this case is obviously to develop a clinical diagnosis strategy that could permit to adequately appreciate the potential thermogenic vulnerability of these individuals. As recently reviewed (1), numerous methodological approaches have been used for this purpose and many of them have allowed the demonstration of a decreased thermogenic component in obese subjects, particularly when tested in a weight-reduced obese state. However, in our opinion, this is again the comparison of an energy expenditure-body weight (or its components) regression line that seems to have had the greatest discrimination potential. In a well cited study, Leibel et al (2) showed that in response to both underfeeding and overfeeding, the measured change in RMR substantially exceeded the change that was predicted by the pre-treatment regression equation linking energy expenditure and the subject’s morphological profile. Our studies have also demonstrated that a weight-reducing program induced a greater than predicted decrease in energy expenditure in obese individuals that was substantial at rest and during exercise. In some patients, this adaptive decrease in thermogenesis was sufficient to entirely compensate for the decrease in energy intake prescribed by the dietitian supervising the program. Interestingly, the factor that was found to explain the greatest part of this effect was the increase in the concentration of plasma organochlorines that generally occurs with the decrease in their dilution space, i.e. body lipids. This effect is maybe not so surprising since animal research has clearly established that organochlorine compounds negatively alter thyroid function and mitochondrial functionality.

Recent investigations have also emphasized clinically meaningful variations in energy expenditure which are not only related with the energy balance and body composition of some patients but which can also increase their risk of premature death. This is the case for individuals exhibiting chronic obstructive pulmonary disease which promotes a hypermetabolic state favoring extreme leanness and death.
In conclusion, adaptive changes in energy expenditure appear to be much more important under some circumstances than what has been generally believed by health professionals and scientists. For the weight-reduced obese person, this may explain his/her resistance to further lose fat that may highlight a protective role of body fat on body homeostasis, particularly regarding the storage of lipid soluble chemical pollutants.

References:


Brown adipose tissue as a potential mechanism for adaptive thermogenesis in humans

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Through the activity of uncoupling protein-1 (UCP1), brown adipose tissue (1) produces heat and thus lowers metabolic efficiency. It is thus the tissue responsible for adaptive adrenergic thermogenesis, i.e. the increase in thermogenesis observed during adrenergic stimulation occurring as a response to chronic cold (2) or chronic exposure to certain diets.

The presence of active brown adipose tissue in adult humans
In humans, active brown adipose tissue has classically been thought to exist only in newborns and to disappear with age. However, there is now unexpected evidence for the presence of active brown adipose tissue in adult humans (3). The original observations stem from studies using 18fluoro-deoxy-glucose positron emission tomography (FDG PET) with the intent to observe tumour metastases. However, symmetrical areas with high FDG (i.e. glucose) uptake were observed in healthy patients; these areas have with time been identified as brown adipose tissue. The activity of these depots is under sympathetic physiological control. This is known from the fact that the sympathetic blocker propranolol inhibits brown adipose tissue activity (FDG uptake), and that the degree of activity is markedly influenced by temperature: brown adipose tissue activity may be observed under normal (i.e. somewhat chilly) examination conditions but the activity is lost when the subject is kept warm during the examination.

Adaptive recruitment of brown adipose tissue has not as yet been demonstrated in adult humans, i.e. there are no convincing studies as yet that demonstrate that the two adaptive conditions that recruit brown adipose tissue in rodents (cold and certain diets) lead to a recruitment of brown adipose tissue in humans, nor are there any studies that demonstrate that adaptation does not take place in adult humans (note the difference between the adaptive recruitment process - where more brown adipose tissue/UCP1 is formed within a time frame of weeks - versus the acute activity where thermogenesis is turned on or off within a time frame of minutes).

Does the FDG uptake really represent brown adipose tissue?
It is well established that the brown-fat depots around the kidney contain UCP1. That the more active brown-fat depots around the clavicle and in the neck also contain UCP1 has recently been confirmed by immunohistochemistry and mRNA measurements.

Does the brown adipose tissue have a principal potential to affect body weight?
According to most present schemes of weight regulation a feedback system regulates the size of our energy stores: the brain receives information on body energy stores (leptin), and food intake and thermogenesis respond accordingly. With such a feedback system, thermogenic alterations should innately be unsuccessful in affecting body weight. There is, however, evidence that increased thermogenesis does lead to body weight reduction. A large number of practical experiments on humans - and a few on experimental animals - clearly show that a mitochondrial uncoupler (dinitrophenol, DNP) applied chronically leads to diminished fat accumulation (4), i.e. there is no compensation through increased food intake. There is now also evidence that a decreased thermogenic capacity leads to obesity. The UCP1 KO mouse has hitherto been reported not to display an obese phenotype, but experiments conducted under thermoneutral conditions, i.e. where metabolism is governed by internal signals rather than by the environment, now clearly demonstrate that absence of UCP1 is sufficient to cause obesity. Again, no compensation through reduced food intake takes place.

Is there evidence that human brown adipose tissue activity affects human weight
The mere presence of brown adipose tissue in adult human of course does not mean that it is important for body weight control. However, there are studies that indicate that this may be the
case. Mutations in the promoter of UCP1 are associated with obesity, at least in certain populations (5). However, brown adipose tissue thermogenic capacity and activity are evidently influenced by other genes in addition to the UCP1 promoter sequences involved in controlling UCP1 expression. There are now also studies that correlate an increased BMI with a decreased brown adipose tissue activity in adult humans. Although both these types of observations are only correlative, the total data now available may be said to indicate that adaptive thermogenesis exists in humans and can thus contribute to (certain cases of) obesity in humans - and that this thermogenesis could potentially be elevated in order to prevent the development of obesity and perhaps also to combat obesity.

References:


Brown adipose tissue (BAT) is a very efficient thermogenic effector, whose role in energy balance has been acknowledged, essentially from works carried in small laboratory rodents. BAT expresses uncoupling protein 1 (UCP1), a mitochondrial protein conferring brown adipocytes with a remarkable thermogenic capacity. UCP 1, which is uniquely expressed in brown adipocytes, is the archetype of uncoupling proteins. Its activation dissipates the proton gradient that builds up across the inner membrane during mitochondrial respiration and that drives ATP production. The dissipation of the gradient prevents ATP synthesis, which results in the accelerated oxidation of substrates and ultimately in an increased production of heat. Up until recently, BAT was not thought to be of importance in man as its existence in the human species was questioned. However, recent findings have reopened the debate regarding the presence of BAT in humans. Positron emission tomography (PET) investigations to trace tumors have shown sites of intense uptake of fluorodeoxyglucose (FDG), which were not tumors and which were ascribed as being BAT. These sites were found in the cervical and subclavicular areas, on each side of the vertebral column, in the mediastinal area and around the kidneys. Our own data from 2556 subjects reveal that factors such as environmental temperature, body mass index, age, and sex determine the presence or the absence of sites showing FDG uptake. Whether BAT can participate to thermogenesis in humans remains to be demonstrated.

The thermogenic activity in BAT strongly depends on the adrenergic stimulation led to by the activation of sympathetic nervous system (SNS), which richly innervates the brown adipocyte. The SNS also controls the thermogenic capacity, which can also be induced by agents such as PPAR gamma agonists. Recent investigations using transneuronal viral retrograde tract tracing have emphasized the rich network of brain regions that innervate BAT. These regions include among other structures the paraventricular hypothalamic nucleus (PVH), the lateral hypothalamus (LH) and the raphe nuclei. Transneuronal viral retrograde tract tracing have also allowed for the characterization of the neurons polysynaptically connected to BAT. PVH neurons expressing the melanocortin receptor 4 and LH neurons expressing melanin-concentrating hormone both connect to the SNS outflow to BAT. The presence of an extensive network of brain structures connecting to BAT reveals the physiological relevance of BAT thermogenesis.
**Skeletal muscle metabolism as a potential mechanism for adaptive thermogenesis in humans**

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Reduction of body weight by 10% or more is accompanied by changes in systemic energy metabolism, neuroendocrine function, and autonomic nervous system physiology, and behavior that act coordinately to return body weight to its initial level 1-5. The major compartment of energy expenditure that is affected following weight loss is energy expended in physical activity 6,7. The decline in energy expended in physical activity persists, even in subjects who have maintained a reduced body weight for 1-6 years 8 and is independent of any changes in time spent in physical activity, per se 2,7,9.

We examined the effects of weight maintenance at 10% below usual body weight on skeletal muscle function in vivo and in vitro. We hypothesized that maintenance of a reduced body weight, would be associated with changes in muscle functional physiology, accounted for by changes in molecular and biochemical characteristics.

We studied subjects as inpatients at their usual body weight and while maintaining a 10% reduced body weight on a liquid formula diet. Maintenance of a reduced body weight is associated with increased skeletal muscle work efficiency independent of body weight, whether measured by bicycle ergometry or NMR spectroscopy at levels of muscle work commensurate with those of daily living. In addition, maintenance of a reduced body weight is associated with a shift in fatty acid oxidative versus glycolytic enzyme activity of skeletal muscle such that fatty acids become the primary muscle fuel substrate at lower levels of activity in reduced weight subjects. The increase in skeletal muscle work efficiency measured by bicycle ergometry in weight-reduced subjects accounts for a significant fraction of the decline in energy expended in physical activity 6,7. We have also found that the maintenance of a reduced body weight is associated with changes in gene expression in skeletal muscle that are concordant with the physiological observation that muscle becomes more chemomechanically efficient. These changes in skeletal muscle at all levels are largely reversed by the administration of “replacement doses” of leptin to weight-reduced subjects.

In summary, we have found that the maintenance of a reduced body weight is associated with changes in skeletal muscle physiology, biochemistry, and gene expression that are in a direction and of sufficient magnitude to account for a significant fraction of the decline in energy expenditure that occurs following weight loss. Skeletal muscle is thus a major “effector organ” for the adaptive thermogenesis that characterizes maintenance of reduced body weight maintenance. The increased skeletal muscle work efficiency that occurs during reduced weight maintenance is leptin-responsive. Pharmacological or behavioral interventions designed specifically to decrease skeletal muscle work efficiency may help to address the high rate of recidivism following otherwise successful weight loss.

**References:**


Adaptive thermogenesis influences body weight regulation

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Following periods of experimental underfeeding \(^1\)-\(^6\) or overfeeding \(^2\)-\(^7\)-\(^{12}\), animals and humans rectify body fat spontaneously. Similar restorations accompany parturition in gravidas.

Mechanical, chemical and genetic interruptions of specific neural and neurohumoral circuits – primarily within the hypothalamus – produce striking changes in body fat. In many instances, these new planes of adiposity are “defended” in the context of experimental under or overfeeding \(^3\)-\(^6\),\(^8\)-\(^{12}\).

Without such regulation, incessant, open loop/unregulated foraging for food would interfere with cognitive development and reproductive activity while unregulated loss of body fat would impair survival and reproduction. Therefore, evolutionary imperatives (survival, reproduction) demand that body fat be regulated; the neural/molecular predicates for doing so have been clearly though not fully demonstrated. In humans, it appears that such regulation is mediated by effects on both energy intake and expenditure, with the former having the predominant role. In rodents, facultative changes in energy expenditure probably play a bigger role than in humans \(^4\).

This regulation is accomplished via a combination of signals relevant to short-term energy status (e.g., blood glucose) and longer term status of whole body energy stores (e.g., leptin). Whether or not adaptive thermogenesis that occurs shortly following weight loss persists over time is a critical question in addressing the high rate of recidivism following otherwise successful weight loss. Research in this area is complicated by difficulties in adequately controlling for multiple critical variables (physical activity, fitness, diet composition, weight stability) over long periods of time in studying subjects who are sustaining weight loss \(^13\). Using a highly controlled in-patient study design, we have found that the same decline in energy expenditure that is evident shortly (1-2 months) after a 10\% or greater body weight reduction is still evident to the same degree in subjects who have sustained similar weight loss for periods of 1-6 years \(^14\). This observation is concordant with studies of self-reported behavioral changes in individuals who are successful in keeping weight off \(^15\).

It seems likely that mammalian and primate/human evolution occurred predominately in environmental circumstances in which sources of calories were at least somewhat limited. Accordingly, mammalian biology of energy homeostasis should favor protection of fat stores over their minimization or disposal.

This asymmetry in the control of body fat stores is, in fact, what is observed in animals and humans \(^16\). Bioenergetic and behavioral homeostatic responses to restriction of available calories is stronger (more resistant to accompanying changes in body fat) than responses to availability of an excess of palatable calories. In contrast to the short- and long- term opposition to sustained weight loss, the increasing prevalence of obesity and the lack of success in reducing weight after it has been gained, indicates that there is relatively little metabolic opposition to sustained weight gain \(^17\),\(^18\).

So, body weight is regulated, but not in a manner comparable to that of – for example - serum sodium, for which both elevations and reductions are met by behavioral responses. Regulation of body weight is more analogous to the behavioral controls of plasma glucose, for which limited or no behavioral responses occur to elevations of blood glucose, but powerful responses occur to critical declines in blood glucose.
References:


Adaptive Thermogenesis does NOT influence body weight regulation

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The energy balance equation is often invoked to frame issues relating to body weight regulation and obesity. The equation states that

\[ \text{Energy Balance} = \text{Energy Intake} - \text{Energy Expenditure} \]

which appears to support the statement that obesity is due to a 'positive energy balance', i.e. that in obesity, energy intake exceeds energy expenditure. Unfortunately, this seemingly obvious pronouncement sets up several misconceptions, which interfere with progress in our understanding of obesity [1].

First, one needs to note that energy is an abstract concept. It is rather the carbohydrate, the fat, and the protein balances which have physiological relevance [2]. It is at their level, and not at the level of the energy balance, that the phenomena important for understanding obesity must be recognized. In adults eating ad libitum, metabolic regulation spontaneously and efficiently adjusts carbohydrate and protein oxidation to their intake. However, this is not the case for fat. Fat balance depends on a number of factors whose interplay ultimately determines body weights and adiposity.

The second unfortunate consequence created by focusing on the energy balance is that in doing so, one confuses past and present. Obese individuals, like lean subjects, tend to reach a state of approximate weight maintenance, with similar daily fluctuations in their energy balances. Thus one fails to recognize that the really important difference between lean and obese individuals is not their prevailing energy balance, but the degree of adiposity at which their food intake tends to cause fat intake to become commensurate with fat oxidation. Why this varies so widely between individuals, and how this is influenced by genetic and by environmental conditions remains the core issue for obesity research.

Particularly relevant to this Symposium is a third misconception promoted by making reference to the energy balance equation, as it makes intake and expenditure appear to be equally significant in determining energy balance. There is, however, a fundamental asymmetry between these two parameters in that changes in resting expenditure can only modestly attenuate the impact of variations in intake, whereas changes in intake can easily compensate for changes in expenditure. And, in fact, they do. Thus, in spite of large differences in energy turnover, weight gains or losses rarely exceed 1 or 2 kg per year during long periods of an individual's life. This reflects an average error of 1-2 % in the adjustment of food intake to energy expenditure. Because this corresponds to daily differences between energy intake and expenditure of only 20 to 40 kcal, it is often claimed that even minor differences between energy intake and expenditure would be able to cause, or to prevent, the progressive development of obesity. For instance, it is widely believed that obesity could be due to unusually low metabolic rates. The fact that energy expenditures per kg of body weight, or per kg of fat-free mass (FFM), are lower in obese than in lean subjects has contributed to this view. It has led to speculations about higher 'metabolic efficiency' in obesity. Such a notion should long have been dispelled by the realization that resting and total energy expenditures are in fact higher in obesity, due to the increase in lean body mass associated with weight gain and the greater costs associated with moving a heavier body.

Arguments about the potential long-term impact of differences in resting energy expenditure, or of small diet-, drug-, or physical training-induced increments in resting energy expenditure, hinge on the assumption that such differences would not be offset by adjustments in energy intake. This is a rather unrealistic assumption! Indeed, there is no reason to think that average energy intakes in subjects eating at their own discretion are 'clamped' at some particular level, particularly when one knows about the large variability in daily food intake (e.g. the intra-individual coefficients of variation for daily food intake average ±23 % [3]).
In effect, some facts speak directly against the notion that minor differences in metabolic efficiency or in resting energy expenditure may be important for body weight regulation.

a) The coefficient of variation for predicting Basal Energy Expenditure (BEE) in adults on the basis of sex, weight, height and age is in the order of ±10 % [4]. When one examines whether deviations of measured BEE (in 432 women and 335 men) from predicted (i.e. 'normal') BEE influence %Body Fat, no hint of a correlation can be detected (R^2 < 0.0002)[4].

b) Stature, which is positively correlated with resting and with total energy expenditures, has no impact on %Body Fat [5].

In conclusion, the fact that differences in resting energy expenditure have no impact on adiposity argues strongly against the view that differences in adaptive thermogenesis, which are of limited scope in man and occur only occasionally, could play a significant role in preventing or promoting the preponderance of obesity.

References:


1. About ADAPTIVE THERMOGENESIS

The oxidation of macronutrients in the body (glucose, fatty acids and amino acids) generates reducing equivalents (e.g. NADH, FADH2), whose re-oxidation is primarily mediated by the enzymes and electron transmitting complexes located in the mitochondria. About two thirds of the energy liberated in this process of ‘oxidative phosphorylation’ can be recovered as high-energy bonds in ATP formed from ADP and Pi, while one third appears as heat. ATP is constantly turned over and when it is used to drive chemical reactions in the body, most of the energy contained in the high-energy bonds is also converted into heat, except for the portions expended to perform physical work or to synthesize exported molecules, i.e. as during lactation. If substrate oxidation takes place without being coupled to ATP regeneration, the energy content of the oxidized substrates is liberated during the oxidative reactions themselves. Thus most of the energy liberated by substrate oxidation is converted into heat, whether or not ATP turnover is involved in the process.

At rest, the ATP turnover needed to sustain the body's basic functions leads to the production of heat at a rate of about 0.8-1.5 kcal/min in adults. The body effectively regulates the release of this heat to the environment, so that the amounts of heat produced as a by-product of metabolism is sufficient under most circumstances to maintain body temperature. The term ‘thermogenesis’ is generally reserved to describe increments in substrate oxidation and heat production under unusual circumstances. For instance, in response to cold exposure, ‘cold-induced thermogenesis’ is engaged through shivering or non-shivering responses. The temporary increase in energy expenditure after meals known as the ‘thermic effect of food’ (TEF) is due mainly to the metabolic cost of absorbing, transporting and storing the nutrients. Increments in energy expenditure during periods of sustained overeating have been extensively studied in animals and man. To the extent that they exceed the effect of TEF and the impact of the concomitant increases in body size, overeating-induced increments in resting energy expenditure are generally regarded as reflecting adaptive mechanisms serving to dissipate some of the energy consumed in excess. This phenomenon is therefore referred to as ‘adaptive thermogenesis’. Conversely, resting energy expenditure declines during food deprivation or starvation. To the extent that this decrease cannot be explained by the reduction of the TEF and by the decline in the size of the body's tissues and organs, the decrease in energy turnover also appears to reflect an adaptive phenomenon, serving in this case to reduce the energy deficit. It is therefore
commonly considered to reflect another aspect of adaptive thermogenesis. However it is not established whether the same mechanisms are involved when adaptive thermogenesis serves to dissipate excess energy intake or to reduce negative energy balance during reduced or insufficient energy intake.

One can also conceive that an adaptative thermogenesis component exists for the response to some drugs and to exercise. Again, in both cases, the effects could translate in augmented or diminished thermogenesis beyond the predicted energy expenditure.

Evidently, the word thermogenesis can promote confusion, unless the aspect being considered is clearly delineated.

2. Proposed definition

Adaptive thermogenesis describes the changes in energy expenditure not attributable to the changes in the size of the body and its tissue composition in response to alterations in energy balance resulting from excess caloric intake, caloric restriction, increase or decrease in exercise levels, cold or heat exposure, drugs and other agents.

3. Purpose of the Symposium

The purpose of this Symposium is:

1. to discuss and finalize the definition of adaptive thermogenesis;
2. to examine the scope of adaptive thermogenesis in man;
3. to delineate its impact on the rate of weight change during overfeeding, caloric restriction, exercise or temperature changes;
4. to describe the mechanisms involved in this phenomenon;
5. to assess its significance in the development and preponderance of obesity in human populations.

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