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Leptin and energy restriction induced adaptation in energy expenditure

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ABSTRACT

Background. Diet-induced weight loss is accompanied by adaptive thermogenesis, i.e. a disproportional reduction of resting energy expenditure (REE) a decrease in physical activity and increased movement economy.

Objective. To determine if energy restriction induced adaptive thermogenesis and adaptations in physical activity are related to changes in leptin concentrations.

Methods. Eighty-two healthy subjects (23 men, 59 women), mean ± SD age 41 ± 8 years and BMI 31.9 ± 3.0 kg/m^2, followed a very low energy diet for 8 weeks with measurements before and after the diet. Leptin concentrations were determined from fasting blood plasma. Body composition was assessed with a three-compartment model based on body weight, total body water (deuterium dilution) and body volume (BodPod). REE was measured (REEm) with a ventilated hood and predicted (REEp) from measured body composition. Adaptive thermogenesis was calculated as REEm/REEp. Parameters for the amount of physical activity were total energy expenditure expressed as a multiple of REEm (PAL), activity-induced energy expenditure divided by body weight (AEE/kg) and activity counts measured by a tri-axial accelerometer. Movement economy was calculated as AEE/kg (MJ/kg/d) divided by activity counts (Mcounts/d).

Results. Subjects lost on average 10.7 ± 4.1% body weight ($P < 0.001$). Leptin decreased from 26.9 ± 14.3 before to 13.9 ± 11.3 μg/l after the diet ($P < 0.001$). REEm/REEp after the diet (0.963 ± 0.08) was related to changes in leptin levels ($R^2 = 0.06$; $P < 0.05$). There was no significant correlation between changes in leptin concentrations and changes in amount of physical activity. Movement economy changed from 0.036 ± 0.011 J/kg/count to 0.028 ± 0.010 J/kg/count and was correlated to the changes in leptin concentrations ($R^2 = 0.07$; $P < 0.05$).

Conclusion. During energy restriction, the decrease in leptin explains part of the variation in adaptive thermogenesis. Changes in leptin are not related to the amount of physical activity but could partly explain the increased movement economy.

1. Introduction

Energy restriction induced weight loss is characterized by changes that promote a positive energy balance and cause the susceptibility for weight regain. On one side, appetite is elevated until the lost weight is regained [1–4]. On the other side, a decrease in total energy expenditure is often described. Studies performed in lean and obese subjects have shown

Abbreviations: TEE, total energy expenditure; REE, resting energy expenditure; AEE, activity induced energy expenditure; FFM, fat free mass; FM, fat mass; PAL, physical activity level.

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significant reductions in resting energy expenditure (REE) during and shortly after weight loss, to values below predictions based on weight loss and body composition changes [5–10]. The decrease in REE beyond what can be predicted by the loss of fat-free mass (FFM) and fat mass (FM) is defined as adaptive thermogenesis. Additionally, several studies demonstrated a decrease in physical activity and activity induced energy expenditure (AEE) as a result of weight loss [11–15] as well as increased movement economy and skeletal muscle work efficiency [5,16]. Leibel stated that the hyperphagic, hypometabolic phenotype of weight-reduced humans is similar to that of leptin-deficient or leptin-unresponsive rodents [17].

Energy restriction and maintenance of reduced body weight are accompanied by declines in circulating leptin concentrations [18]. This reduction in leptin is seen with different protocols to induce weight loss, indicating a consistent effect [19,20]. Experiments in mice revealed that part of the physiological response to weight loss can be prevented by leptin injections [21]. Subsequent research in humans has indicated that administration of leptin that restores circulating leptin to levels present before weight loss reversed the increased energy intake [22] and decreased energy expenditure [23] as well as changes in sympathetic nervous system tone, thyroid function and movement economy [24]. It is now believed that leptin or similar drug treatment may decrease or diminish the negative physiological consequence of energy restriction and could lead to more successful weight maintenance [25].

Linking adaptive thermogenesis, the decrease in physical activity and increased movement economy to changes in leptin concentrations during weight loss will give further insight in the underlying mechanisms and the pharmacotherapeutic relevance of the focus on leptin. The aim of this study was to determine if energy restriction induced adaptive thermogenesis, change in physical activity and increased movement economy is related to changes in leptin concentrations.

2. Subjects and Methods

2.1. Subjects

Eighty-two healthy subjects (59 women and 23 men) with a mean age of 41 ± 8 years and with a mean body mass index (BMI) of 31.9 ± 3.0 kg/m^2 were recruited by advertisements in local newspapers and on notice boards at the university. They underwent an initial screening that included measurements of body weight and height and the completion of a questionnaire on general health. All were in good health, not using medication (except for contraception), nonsmokers and at most moderate alcohol consumers. They were weight stable as defined by a weight change <5 kg for at least 3 months prior to the study. The study was conducted according to the guidelines laid down in the Declaration of Helsinki and procedures were approved by the Ethics Committee of the Maastricht University Medical Centre. Written informed consent was obtained from all participants.

Clinical Trial Registration Number: NCT01015508 at clinicaltrials.gov.

2.2. Study Design

The study consisted of a very low energy diet for 8 weeks. Subjects came to the university for measurements on two occasions: the day before the start of the diet (baseline) and 8 weeks after the start of the diet (end of the diet). On each occasion, measurements included REE followed by body composition and the collection of a blood sample and were performed from 8:00 in the morning onwards in the fasting state. Total energy expenditure (TEE) and activity counts were measured during the two weeks prior to each measurement point.

2.3. Diet

The weight loss diet (Modifast; Nutrition et Santé Benelux, Breda, The Netherlands) was followed for a period of 8 weeks. The diet was a protein-enriched formula that provided 2.1 MJ/day (51.9 grams of protein, 50.2 grams of carbohydrates and 6.9 grams of lipids) and a micronutrient content, which meets the Dutch recommended daily allowance. The very low energy diet was provided to the subjects as sachets with powder. Each sachet represented one meal and 3 sachets were consumed every day. Besides the provided meal-replacements, subjects were allowed to eat vegetables when feeling hungry. Subjects were instructed to mix the powder with the amount of water indicated on the packages and were advised to drink water sufficiently throughout the diet period.

2.4. Body Composition

Height was measured at screening to the nearest 0.1 cm with the use of a wall-mounted stadiometer (model 220; Seca, Hamburg, Germany). Body composition was determined according to Siri's three-compartment model based on body weight, body volume and total body water [26]. Body weight was measured using a calibrated scale (Life Measurement Corporation, Concord, CA). Body volume was measured via air-displacement plethysmography with the BodPod System (Life Measurement Corporation) [27,28]. Total body water was determined using deuterium dilution during the preceding night, according to the Maastricht protocol [29]. Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2).

2.5. Energy Expenditure

To reach the university for REE measurements, subjects were instructed to travel by public transport or by car to avoid physical activity that would increase REE. After arrival, they rested on a bed for 30 minutes, followed by 30 minutes of measuring their REE in the supine position using an open-circuit ventilated hood-system [30]. Gas analyses were performed by a paramagnetic oxygen analyzer (Servomex, type 500A, Crowborough, East Sussex, UK) and an infrared carbon dioxide analyzer (Servomex, type 500A, Crowborough, East Sussex, UK) while flow was kept at a constant rate of 80 l/min and additionally measured as described by Schoffelen et al. [31]. The within individual coefficient of variation for this system is 3.3% ± 2.1 [30]. Calculation of REE from measured oxygen consumption and carbon dioxide production was based on Brouwer's formula [32].