비만/대사증후군에 대한 적응열발생 가설

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An Adaptive-thermogenesis hypothesis for the mechanism of obesity/metabolic syndrome

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1. Introduction

Obesity and its related disorders such as metabolic syndrome and hypertension are the major risks to human life. Although much is known about its biochemical mechanisms, little attention was paid to the biophysical nature of obesity, a state of increased body mass. Basically body mass is determined by the balance between energy intake and energy expenditure. Though many experimental studies on the energy balance in obesity have been conducted, a defect in metabolic mechanisms that control energy expenditure has not been described in human obesity (Kopelman, 2000). In this study we presented an adaptively thermogenesis hypothesis for obesity, integrating scaling law, temperature homeostasis and energy conservation.

Obesity is characterized by elevated fasting plasma insulin and an exaggerated insulin response to an oral glucose load, in short, a state of insulin resistance (Kolterman et al, 1980). We previously showed evidences that the composite state of cellular mitochondrial DNA in quality and quantity of an individual is determinant of insulin resistance state, and thrifty phenotype, a related condition which predisposes to insulin resistance state (Lee, 1999 and Lee et al., 2005, Taylor et al 2005). Recent studies by Peterson et al (2004) and Lowell and Shulman (2005) had established without doubt that mitochondrial dysfunction is related to insulin resistance. Recently we extended the concept further and proposed a mitochondria-based model for insulin resistance syndrome (Lee et al., 2005). We suggested that this mitochondria based model would be compatible not only with already known biochemical features, but the biophysical law of allometric scaling.

Integrating the allometric scaling law of body weight, energy conservation equation, and adaptive thermogenesis relations, we developed a new computational model to analyze the mechanisms of obesity. As a corollary, we propose an adaptive thermogenesis hypothesis for the pathogenesis obesity; decreased heat generation due to impaired mitochondrial function needs compensatory mechanism for more heat generation and decreased heat dissipation to maintain optimal core temperature, which induces eventual body weight gain. We pay attention to the previous reports by Rising et al. (1992, 1995), who showed low body core temperature might be a sign of an obesity-prone syndrome in human. We also note that Jequire et al. (1974) reported an increased in thermal body insulation is generally found in obese peoples, implying that the decreased energy production in obese peoples is compensated by a decreased energy dissipation to environment. One might consider this new formulation as a special case of allometric scaling law applied to human. This can also be considered as an extension of our mitochondria-based model, which was descriptive and stayed at conceptual level, to quantitative terms.

To verify the proposed model, we adopted known physiological variables to the model and then computed results were compared with the results observed in Pima Indians (Leiberl et al. 1994, Ravussin et al., 1988) and other reports in animal (Mitchel and Keesey, 1977).

2. Theoretical method

A schematic diagram of the present adaptive thermogenesis model is depicted in Fig. 1, representing three basic principles: energy conservation law, metabolic scaling law, and core temperature homeostasis. Body weight change is derived from the energy conservation law whereas the core temperature homeostasis is described by the scaling law and the long-term adaptive

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thermogenesis principle.

2.1 Energy conservation law

A quantitative relation involved in energy balance is described using the expression proposed by Christiansen et al. (2002). According to the study, the conservation of combustible energy leads to the following differential equation of body weight change:

$$\frac{dM}{dt}=\frac{1}{c}\left(EI-PAL\cdot REE\right) \tag{1}$$

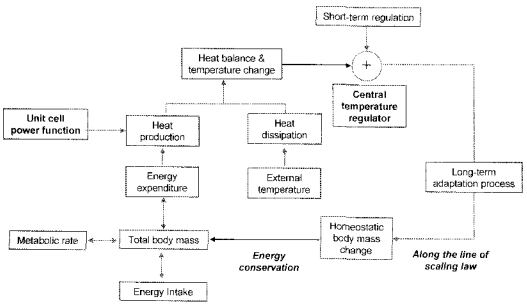


Fig. 1 Schematic of the present themogenesis hypothesis on obesity

Here, M is body weight (unit : kg), EI is energy intake (unit: MJ/day), TEE is total energy expenditure (unit: MJ/day), REE is resting energy expenditure (unit: MJ/day), and PAL means a physical activity level that is expressed as TEE divided by REE. The variable c in Eq. (1) is as follows:

$$c=cl+(cf-cl)\cdot f0 \tag{2}$$

$$f_0=\frac{\Delta BF}{\Delta M} \tag{3}$$

where BF represents body fat, f0 is the ratio of BF change on M and cf , cl denote the content of combustible energy per kg fat tissue and per kg lean tissue, respectively. Though the fat weight of human remains constant at control condition, the variation in body fat composition (the ratio of fat to lean mass) during obesity development is not negligible and we modeled this using Eq. (3) and the following equation (Forbes, 1987).

$$\frac{d(FFM)}{dM}=\frac{k}{BF+k} \tag{4}$$

where FFM means a fat free mass. Therefore, the time derivative of body fat is expressed as follows:

$$\frac{d(BF)}{dt}=\frac{dM}{dt}\cdot\frac{d(BF)}{dM}=\frac{dM}{dt}\cdot\frac{BF}{BF+k} \tag{5}$$

The difference between energy intake and consumption induces body weight change as shown in Eq. 1. In case the feedback mechanism for temperature homeostasis is activated, the EI, PAL can be changed by the mechanism while REE is approximately same with body metabolic rate (BMR) governed by body weight (West et al., 1997). If we separate the EI and PAL into "static" and "variant"due to homeostasis, then Eq. (1) can be rearranged follows :

$$\frac{dM}{dt}=\frac{1}{c}\left(EI_{st}-PAL_{st}\cdot BMR\right)+\frac{1}{c}\left(\Delta EI-\Delta PAL\cdot BMR\right) \tag{6}$$

In case energy intake is controlled, the term ΔEI will be zero. Since the 2nd term of the RHS in the above equation is mainly due to homeostasis effect, we set this as follows:

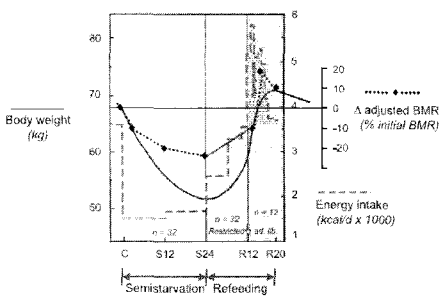
$$\frac{dM}{dt}=\frac{1}{c}\left(EI_{st}-PAL_{st}\cdot BMR\right)+\left(Homeostasis\ effect\right) \tag{7}$$

For simplicity we omit the subscript 'st'.

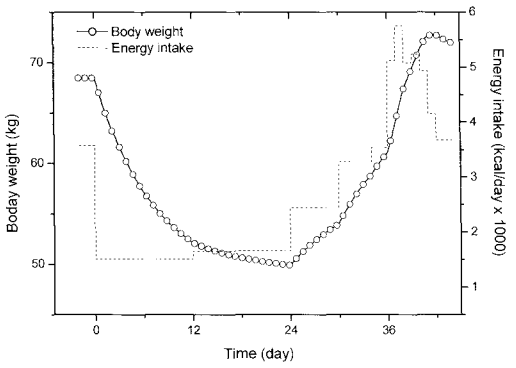
3. Results

3.1 Baseline simulation result

For validation of the present approach, The Minnesota experiment on human semistarvation and refeeding was performed to assess the effect of homeostatic regulation on energy conservation. The experimental results of Keys et al. (1950) were redrawn in Dulloo et al. (2004). Semistarvation of the subjects by reducing their daily energy intake for several weeks induced an immediate decrease in body weight, but this weight decrease was attenuated later in the period of semistarvation. Subsequently, weight was restored quickly upon ending the calorie restriction. Upon being permitted to feed freely, hyperphagia was observed, and the subjects fell into a "yo-yo" state in which they gained weight beyond their initial weight (Fig. 2(a)). To mimic this case, we used the experimental energy intake and 1.3 as the physical activity level. Fig 2(b) shows the simulated result, in which a pattern similar the experimental pattern is observed.



(a) Human experiment by Dulloo et al. (2004)



(b) our simulation results.

Fig. 2 Qualitative comparison with the caloric restriction test in the Minnesota experiment on human semistarvation and refeeding (Dulloo et al., 2004).

3.2 Effect of basal metabolic rate to obesity

Though the results are demonstrating indirectly the validity of the temperature hypothesis by proper reproduction of the experimental results, we simulated the effect of the altered BMR on body weight change (Ravussin et al., 1988) and assessed the sequential events related to it. For the setting of baseline condition (standard case) matched with the experimental condition of Ravussin et al., we assume a slight increase of energy intake inducing

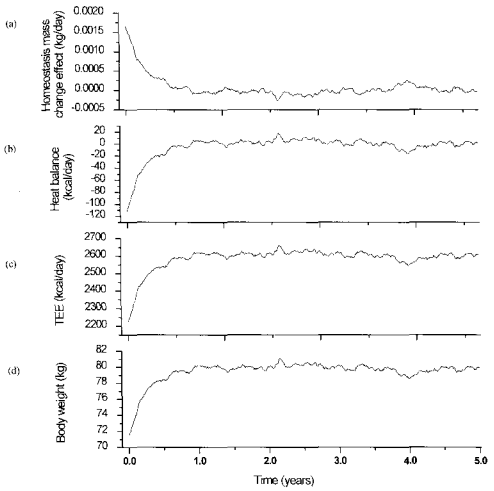


Fig. 3 Sequential events of decreased BMR effect on body weight. (a) Homeostasis weight change during the BMR decrease by -200 kcal/day, (b) Heat balance change during the BMR decrease by -200 kcal/day, (c) TEE change, (d) Body weight change.

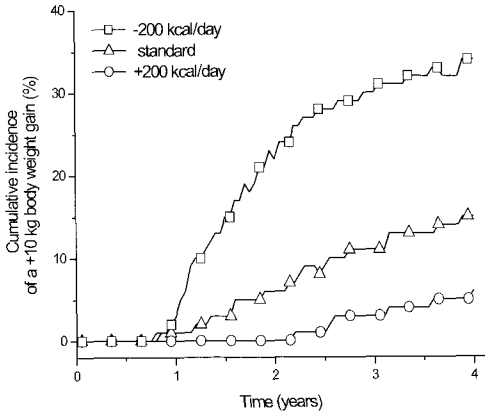


Fig. 4. Effects of the altered BMR on body weight change. For standard case (without variation of BMR), body weight increased slightly for 4 years. The augmented body weight increase was induced by the BMR decrease of 200 kcal/day whereas body weight increase was delayed by the BMR increase of 200 kcal/day.

about 12% increase of body weight for 4 years. From this standard condition, increase and decrease of BMR by 200 kcal/day are invoked to assess the effect of altered BMR on body weight. Sequential events of decreased BMR effect on body weight are shown in Fig. 3. Homeostasis weight change due to the BMR decrease by -200 kcal/day was maximal and decreasing according to time, reaching to steady state value of zero (Fig. 3(a)). Heat balance change and TEE change were increasing from the minimum values in initial state (Fig. 3(b), (c)). An increase of body weight due to decrease BMR was shown in Fig. 3(d). Cumulative incidence of a 10 kg body weight change due to altered BMR was plotted in Fig. 4. For the standard case (without variation of BMR), body weight increased slightly for 4 years. The augmented body weight increase was induced by the BMR decrease of 200 kcal/day whereas body weight increase was delayed by the BMR increase of 200 kcal/day.

4. Conclusions

In this study, we presented a newly developed computational model to analyze the mechanisms of obesity and proposed adaptive thermogenesis hypothesis of obesity. A new mathematical model incorporating a stochastic process of variable uncertainty was also formulated to verify the hypothesis. The method is based on the energy

conservation law, the allometric scaling law on body weight, and the principle of homeostasis of body core temperature. According to the theory, a disturbance in heat production or dissipation induces the energy unbalance and so body weight change as a compensatory mechanism is augmented. This mechanism is verified in the simulation results compared with experimental results. In the short term starvation study, the simulated results show that the energy balance breaks due to decreased energy intake and body weight increases . Animal experiment showing an abrupt recovery of body weight by a diet restriction-refeeding protocol is successfully reproduced using the present method . Effect of altered body weight on basal metabolic rate (BMR) is tested and the results are compared with the previous experiment. 10% weight gain induced a right-upward shift of data points in the graph of BMR to fat free mass. On the contrary, a left-downward shift of data points was observed for 10% weight loss. Sequential events of decreased BMR effect on body weight were delineated indicating the validity of the present hypothesis . Cumulative incidence of a 10 kg body weight change due to altered BMR was well matched with the experiment and demonstrated that the broken energy balance augments obesity by sequential events from heat balance, scaling law to energy conservation equation.

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